Patient Related Outcome Measures

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REVIEW

Patient-Reported Outcomes Associated with Treatments for Testicular Cancer: A Systematic Review

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Background: Testicular cancer and its treatment can have major short- and long-term effects on the health-related quality of life of those affected. This systematic review aims to summarise patient-reported outcome (PRO) data concerning health-related quality of life, functional impacts and common side-effects of treatments for testicular cancer.

Methods: We systematically searched Medline OVID, CINAHL, PubMed, Embase and the Patient-Reported Outcomes Over Time In Oncology (PROMOTION) databases from inception to 25 March 2020, using "testicular cancer" and "PRO" search terms developed in conjunction with a medical librarian. Two authors screened abstracts and full-text articles for studies that reported primary PRO data related to the treatment of testicular cancer including at least 50 participants. We excluded psychosocial data as this was included in our companion review. Data were extracted by three reviewers, and quality was assessed by two reviewers using QUAL-SYST. Studies with a quality of score over 65% were included in our narrative synthesis.

Results: A total of 1831 records were identified via our database searches and 41 met inclusion criteria. Of these, 35 included participants who had chemotherapy. Twenty-eight different PRO measures were used across the 41 studies. Of the 41 studies, 29 had quality scores over 65% and were included in our narrative synthesis. We found that chemotherapy was generally associated with a higher side-effect burden than other treatments, and higher burden was associated with higher doses of chemotherapy. Hearing problems, peripheral neuropathy, and Raynaud's phenomena were particularly common side-effects. Problems with sexual functioning were associated with chemotherapy, radiotherapy and surgery.

Discussion: While many studies found that between-treatment differences resolved within the first 12 months since diagnosis, there were many long-term and dose-dependent impacts associated with chemotherapy and radiotherapy across PRO domains. Offering information about these aspects, and information about expected survival outcomes, will help inform, prepare, and empower patients to make decisions about treatment aligned with their preferences and personal situations.

Keywords: testicular cancer, patient-reported outcomes, quality of life, cancer survivorship

Introduction

Testicular cancer is the most common cancer diagnosis among young men aged 15–40 years.[1,2] Although it is a relatively rare cancer, incidence is increasing worldwide, particularly in Western Europe, Northern Europe, Australia and New Zealand.[2] Treatment for testicular cancer typically involves orchiectomy (ie, removal of the affected testicle), followed by surveillance, with or without

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chemotherapy, radiotherapy or retroperitoneal lymph node dissection (RPLND), depending on the diagnosis and stage of disease,[3] and patient and clinician preferences. Treatments for testicular cancer are highly effective, particularly for earlier stages of disease. Overall survival rates are high, with 94.9% living more than five years post diagnosis, and five-year survival rates have steadily been increasing since the 1970s.[4] The five-year relative survival rate for localized testicular cancer, accounting for 67.8% of cases, is 99.0%.[4] The health-related quality of life (HRQOL) of survivors is therefore a primary concern. Each treatment is associated with side-effects that manifest during active treatment or after completion, and can persist for years hence; sometimes for life.

For example, impaired fertility may become evident after orchiectomy.[5,6] Men who have had a bilateral orchiectomy will not be able to conceive a pregnancy unless semen samples were stored prior to surgery. Neural damage following RPLND and cumulative doses of chemotherapy can also lead to fertility issues.[7] Body image issues are also commonly reported following orchiectomy, due to changes in physical appearance after removal of a testicle, which can impact psychological wellbeing, self-confidence, sexual functioning and perceptions of masculinity.[8] Cisplatin-based chemotherapies have been associated with hearing loss, Raynaud's phenomena, peripheral neuropathy and cardiovascular disease.[9,10] Radiotherapy has been associated with gastrointestinal complaints in the long term.[11] There is equivocal evidence for the impact of some treatments on survival, for example, surveillance versus a single cycle of carboplatin for the treatment of patients with Stage I disease; therefore, data about the impact of treatment side-effects is particularly important.

Given the young age of affected men, long-term side-effects of treatments for testicular cancer have great potential to affect the HRQOL of survivors for much of their adult life. HRQOL is defined as "the subjective assessment of the impact of disease and treatment across the physical, psychological, social and somatic domains of functioning and wellbeing".[12] Fertility, body image and sexual functioning concerns can be particularly concerning for men seeking a partner, or wanting to start or grow their families.

Research evidence about the impact of different treatments on aspects of functioning, HRQOL and other patient-reported outcomes (PROs) provides essential information to help newly diagnosed men decide on treatment options, and/or be prepared for the impact of their treatment. This systematic review aims to summarise PRO data concerning the impact of various treatments for testicular cancer. PROs are defined as any report about the status of a patient's health that comes directly from the patient, without interpretation by anyone else.[13] We do not report psychosocial outcomes in this review, as they have been addressed in a companion paper.[14]

Methods

Our methods follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[15]

Search Strategy

Medline OVID, Cumulative Index to Nursing and Allied Health Literature (CINAHL), PubMed, Embase and the Patient-Reported Outcomes Over Time In Oncology (PROMOTION) (http://promotion.gimema.it/) databases were systematically searched from inception to 25 March 2020, using a search strategy developed in collaboration with an academic librarian. The search terms combined PRO and testicular cancer terms (see Appendix 1). Duplicate entries were identified in Endnote X9 and removed.

Study Screening

Two authors independently screened all abstracts according to pre-established eligibility criteria. Both authors completed a pilot-screening exercise of 200 papers to determine agreement and test the eligibility criteria before screening the remaining abstracts. Full-text papers were checked against the same eligibility criteria, with the addition of one further exclusion criterion (see below).

Eligibility Criteria

Studies were included if they reported primary PRO data related to the therapeutic treatment of testicular cancer. Studies with: samples including other cancer diagnoses, less than 50 patients, patient-reported psychosocial data only, psychosocial or complementary alternative medicine (CAM) interventions, qualitative data only, conference abstracts, research commentaries, systematic reviews, non-English reports and PRO measure validation or methodological papers were excluded. At the full-text stage, we also excluded studies if PRO data were not reported by treatment received, in both single- and multi-arm studies. If a study reported psychosocial outcomes in addition to

other PROs, the psychosocial data were excluded (as it was captured by our companion review),[14] while the other relevant data were included.

Data Extraction

The following data were extracted from each publication by one of three reviewers (RMB, SKN, OR): study design, sample size, stage of disease, recruiting countries, recruitment period, participant age at diagnosis and at survey completion, primary endpoint, PRO objectives, treatments received, PRO measures used, PRO domains reported, time points with PRO data reported, summary of key PRO findings for each treatment group.

Assessment of Research Quality of Included Studies

Two reviewers (SKN, OR) assessed the quality of studies using QUAL-SYST criteria.[16] Studies that scored a total of 65% or higher (of applicable items) are the focus of our review. This cut off was chosen with the intention of being inclusive, but not too liberal, based on Kmet's guide that 55% is considered "relatively liberal".[16]

Narrative Synthesis

Key findings comparing the PROs between treatment groups were extracted and described for this review using the narrative synthesis technique. Due to differences in the study design, measures, and analyses among the included studies, the nature of information available in each study manuscript varied, ranging from mean differences of scale scores, regressions or other multivariate comparisons, or raw scale scores for each PRO domain.

Results

A total of 1831 records were identified via our database searches, as shown in Figure 1. After duplicates were removed, 1406 abstracts were screened, and 195 full-text articles were checked. Forty-one articles met inclusion criteria (listed in Appendix 2).

Studies

Of the 41 studies, 36 described PROs associated with chemotherapy, 23 described PROs associated with radiotherapy, 15 for surveillance, 14 for RPLND, and four studies described PRO for surgery without specifying the nature of surgery. Studies recruited largely from Western Europe (n=27), followed by the UK (n=8), Australia/New Zealand (n=5), North America (n=4), Asia (Japan only, n=3), and Eastern Europe (n=2). The most common study design was cross-sectional (n=22), followed by longitudinal non-randomised studies (n=8), randomised controlled trials (n=5), case-control studies (n=2), retrospective studies (n=2), pilot study (n=1) and a pooled analysis of RCT data (n=1).

Excluding psychosocial measures, 14 different validated PRO measures and 13 study-specific measures were used. The most commonly used PRO measures were the European Organisation for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core (QLQ-C30)[17] (n=14), Short Form-36 (SF-36)[18] (n=9), Scale for Chemotherapy-Induced Neurotoxicity (SCIN)[19] (n=6), EORTC QLQ-TC26 testicular cancer module[20] (n=5), Swedish Health-Related Quality of Life Survey (SWED-QUAL)[21] (n=2) and The Gothenburg Quality of Life Instrument[22] (n=2). All other measures were used in just one study.

A summary of PRO findings is presented in Table 1. Due to most studies describing PROs associated with chemotherapy, we have presented the table in two groups: studies including chemotherapy and studies not including chemotherapy. Of the 41 studies, 29 scored above our QUALSYST quality score threshold of >65%[9,11,19,23–48] and PRO findings are described below. We have categorised these outcomes as they were reported in the source papers, even if some of the groupings seem arbitrary or mechanisms might be different.

Neurotoxicity, Raynaud's and Related Phenomena

Chemotherapy Dose-Induced Neurotoxicity and Raynaud-Like Phenomena

Among the 26 higher quality studies including a chemotherapy treatment group, higher doses of chemotherapy were generally associated with higher self-reported neurotoxicity.[9,19,23,24,28] Specifically, Oldenburg 2007 (N=238) found that cumulative dose of cisplatin was significantly associated with paraesthesia in the toes ($p<0.001$) and Raynaud-like phenomena in the toes ($p<0.001$). The risk of a more severe symptom class increased by roughly 1.3 for each step of 100 mg/m2 cumulative cisplatin, the dose corresponding to one cycle of chemotherapy.[9] Similarly, Sprauten (N=169) reported that total SCIN score was positively associated with administered cisplatin dose ($p=0.016$), dose-intensive therapy

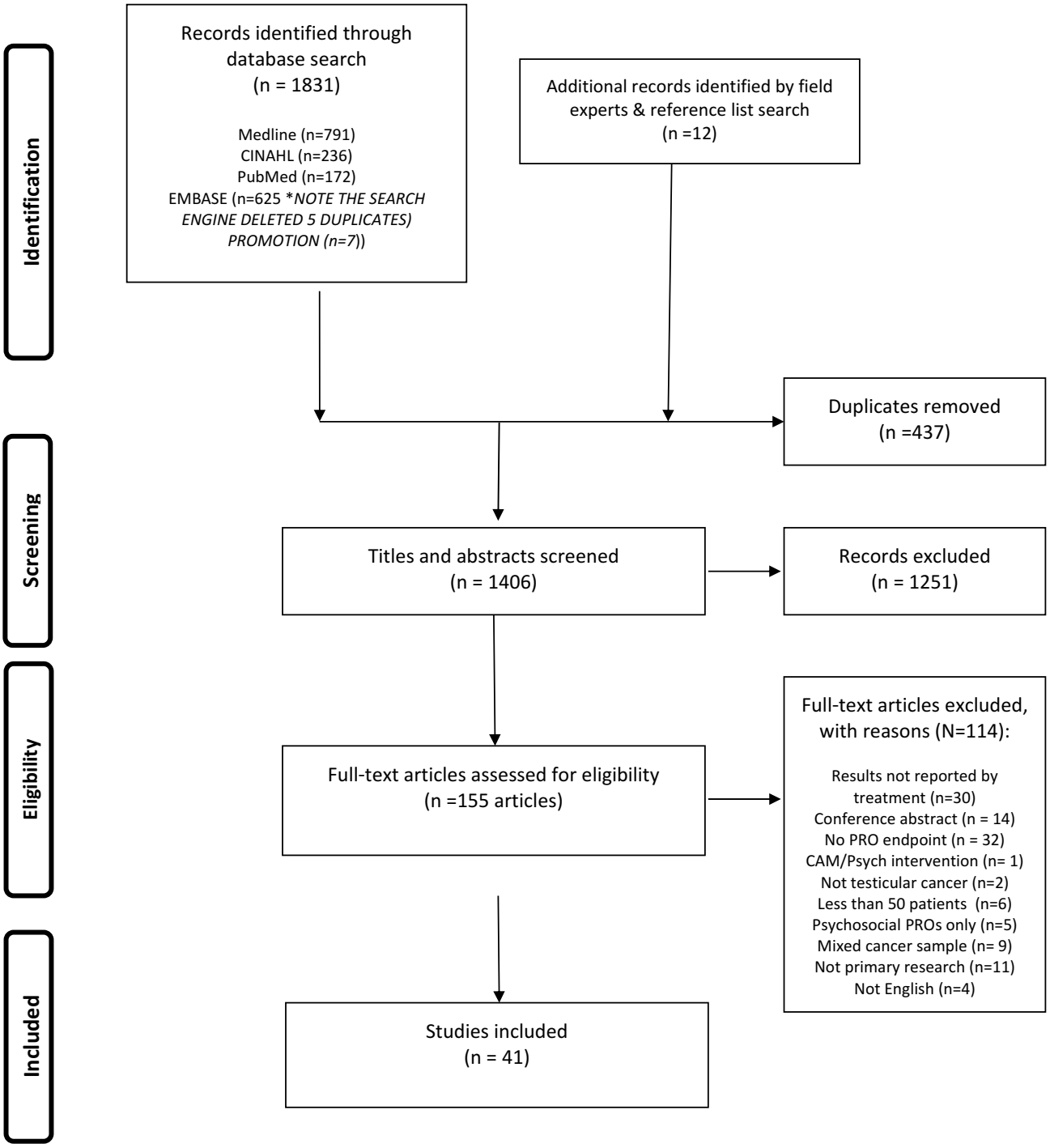

Figure 1 PRISMA flow diagram.
Notes: PRISMA figure adapted from Moher D, Liberati A, Tetzlaff J, Altman DG; The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses:the PRISMA statement.
PLoS Med. 2009;6(7):e1000097. Creative Commons

(p=0.032), and age at survey (p=0.035) in univariate but not multivariate analyses.[44] Glendenning and colleagues (N=739) also found that peripheral neuropathy increased significantly with increased cisplatin dose.[28] In another study (N=149), participants randomised to 4 cycles of BEP had higher mean scores for numbness or pins and needles, compared to participants randomised to 3 cycles of BEP, at 6, 9 and 12 months post-randomisation

Table 1 Summary of Included Studies and PRO Findings

Study Reference	Key Details of Study and Sample: • Study Design • Sample Size • Stage of Disease • Recruiting countries • Recruiting Period	Age at Diagnosis; Age at Survey Completion	Objectives	Interventions/ Treatment and N	PRO Measure/s Used	PRO Domains Reported	Time Points with PRO Data Reported (or Time Since Diagnosis or Treatment for Cross-Sectional Studies)	Summary of PRO Results
Studies Including Chemotherapy Interventions								
Arai 1996	Cross-sectional, N= 83, Seminoma and non-seminoma, Stage I–III, Japan, 1993	Overall mean age 33.8 years (Range18 to 60 years) at the time of study	Assess the impact of different treatment modalities on psychofamily well-being wellbeing.	Group 1: Chemo (cisplatin based) = 34 (15 only chemo + 19 also had RPLND). Group 2: RT (infra-diaphragmatic) = 42 Group 3: Surveillance=7	Study-specific questionnaire (not named)	Psychosocial well-being, working ability, satisfaction with life, relationships, and general health and fitness.	Mean time from start of treatment to survey completion was 8 years (Range 1–21.8 years)	Group 1: Chemotherapy Working ability (WA) total score (TS)- 9.5, Sleeping problems (SP)-1.2. Group 2: Radiotherapy WA- 8.8, SP-1.5. Group 3: Surveillance WA-11.4 SP-1.7 Chemotherapy and radiotherapy groups had higher mean working ability total scores than the surveillance group ($p<0.01$). Mean satisfaction with life total scores was higher for chemotherapy and radiotherapy groups than surveillance ($p <0.05$).

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Table 1 (Continued).

Study Reference	Key Details of Study and Sample: • Study Design • Sample Size • Stage of Disease • Recruiting countries • Recruiting Period	Age at Diagnosis; Age at Survey Completion	Objectives	Interventions/ Treatment and N	PRO Measure/s Used	PRO Domains Reported	Time Points with PRO Data Reported (or Time Since Diagnosis or Treatment for Cross-Sectional Studies)	Summary of PRO Results
Brydoy 2009	Cross-sectional study, N = 1409 Seminoma, Non-seminoma. Stage I–IV. Norway (multicentre) 1998–2002.	Median age at treatment 32 years (Range: 15–64 years). At survey: 43 years (Range: 23–75 years)	Assess the occurrence of self-reported paresthesias, Raynaud-like phenomena, tinnitus, and impaired hearing according to treatment.	Divided in 6 group 1. Surveillance: N=119. 2. RPLND: N = 153. 3. RT: N = 609 4. Chemo with one to four cycles of cis-platin: N = 425. 5. Chemo with five or more cycles of cis-platin: N = 46. 6. Dose dense chemo (cis>20 mg/m2 daily): N = 57.	Scale for Chemotherapy-Induced Neurotoxicity (SCIN),	Raynaud-Like Phenomena and Paraesthesia, Hearing Impairment and Tinnitus	Median 10.7 years, Range 4–21 years after orchiectomy.	Neuro and ototoxic side effects and Raynaud-like phenomena were more common in patients treated with four cycles of cisplatin based chemo, several years post treatment. More intensive chemotherapy was associated with more symptoms. Raynaud-like phenomenon. Group 4 - Chemo 1–4 cycles: OR2.9 (95% CI 2.2–3.9) P <0.001. Group 5: 5+ cycles: OR 8.0 (95% CI 4.4–14.7) P<0.001. Group 6, Dose intense: OR 5.7 (95% CI 3.2–9.9) p <0.001. Paraesthesia. Group 4: Chemo 1–4 cycles: OR2 (95% CI 1.5 −2.7), p <0.001. Group 5: 5+ cycles: OR 3.9 (95% CI 2.1–7.3), P<0.001. Group 6 Dose intense: OR 2.3 (95% CI 1.3–4.2), p 0.007.

Bumbasirevic 2013	Cross-sectional study, N= 202. Stage N/R. Serbia 2010.	Mean age at survey 35.5 years (Range 19–66). Mean 47.3 months since treatment.	Assess HRQoL, depression, adverse physical symptoms, and sexual function within a large and representative sample of Serbian long-term TCS and to address cultural specificity.	Adjuvant chemo (type unspecified): N =185 Chemo+RPLND: N =17	SF-36, EORTC QLQ-30, Beck Depression Inventory (BDI).	SF-36 Physical function (PF) Role-physical (RP) Bodily pain (BP) General health (GH) Vitality (VT) Social functioning (SF) Role-emotional (RE) Mental health (MH) Physical component summary (PCS) Mental component summary (MCS) Total score (TOTALSC) EORTC QLQ-C30 Global health status (QL2) Physical functioning (PF2) Role functioning (RF2) Emotional functioning (EF) Cognitive functioning (CF) Social functioning (SF) Fatigue (FA) Nausea and vomiting (NV) Pain (PA) Dyspnea (DY) Insomnia (SL) Appetite loss (AP) Constipation (CO) Diarrhoea (DI) Financial difficulties (FI)	1 year after surgical treatment and platinum based chemotherapy,	Linear regression did not show any influence of treatment type onSF-36 total score (p=0.838). Mean SF −36 (whole sample) PF 89.26 (17.79) RP 76.61 (35.54) BP 84.15 (19.50) GH 74.38 (18.83) VT 72.62 (17.96) SF 81.68 (20.87) RE 74.75 (38.28) MH 76.24 (16.77) PCS 81.10 (18.77) MCS 76.32 (19.30) TOTALSC 78.71 (17.87) Mean EORTC-QLQ C 30 (whole sample) QL2 80.53 (17.88) PF2 91.42 (13.43) RF2 92.66 (16.36) EF 77.89 (21.77) CF 89.93 (17.05) SF 87.05 (22.70) FA 19.75 (20.89) NV 3.13 (7.87) PA 12.62 (16.99) DY 9.08 (17.90) SL 17.49 (27.25) AP 5.61(15.99) CO 3.13 (12.70) DI 5.94 (15.87) FI 16.50 (29.60)

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Table 1 (Continued).

Study Reference	Key Details of Study and Sample: • Study Design • Sample Size • Stage of Disease • Recruiting countries • Recruiting Period	Age at Diagnosis; Age at Survey Completion	Objectives	Interventions/ Treatment and N	PRO Measure/s Used	PRO Domains Reported	Time Points with PRO Data Reported (or Time Since Diagnosis or Treatment for Cross-Sectional Studies)	Summary of PRO Results
Dearnaley 2005	Longitudinal cohort N=115 Non-seminoma. UK	Age N/R	A multicentre Phase II pilot study of two courses of adjuvant BOP, including assessment of toxicity,relapse rate and quality of life (QoL).	Two courses of BOP 14 days apart: cisplatin 50 mgm_2 days 1 and 2, vincristine 1.4 mgm_2 (max. 2 mg) days 2 and 8, bleomycin 30000 IU days 2 and 8.	EORTC QLQ-C30 and QLQ-TC26 testicular cancer module.(in development)	Global health status (QL2) Physical functioning (PF2) Role functioning (RF2) Emotional functioning (EF) Cognitive functioning (CF) Social functioning (SF) Fatigue (FA) Nausea and vomiting (NV) Pain (PA) Dyspnea (DY) Insomnia (SL) Appetite loss (AP) Constipation (CO) Diarrhea (DI) Financial difficulties (FI) And item-level data for the QLQ-TC26.	Pretreatment End of treatment 6 Months posttreatment 12 Months posttreatment 24 Months posttreatment	Relative to baseline, all individual symptom items produced worse scores at the end of treatment assessment, and those significant at the adjusted significance level of o0.001 being hair loss, pain, numbness or tingling in hands/feet and ringing in the ears. Pain/ numbness persisted at the same level of significance at 6 months post-treatment, reducing with time but remaining at the conventional significance level of 5% at 24 months post-treatment.

de Wit 2001	RCT 2×2 factorial design, N= 812 Seminoma and Non-seminoma. Multiple centre (Belgium, Netherlands, Denmark, Germany, Austria, Italy, United Kingdom, Australia, Russia) Stage II/III 1995–1998.	Range 14–63 years	PFS and OS (primary), QoL (secondary)	Randomised to four groups Group 1: 3xBEP for 3 days Group 2:3xBEP for 5 days Group 3: 3x BEP +1xEP for 3 days Group 4: 3x BEP+1xEP for 5 days	EORTC QLQ-C30 and QLQ-TC26 testicular cancer module.	Physical, role, cognitive functioning, fatigue, nausea, vomiting, appetite loss and overall QoL.	Baseline (at randomisation before chemo), 3 months, 6 months, 1 year and 2 year.	3BEP was associated with less pain, numbness, and tingling in hands and feet, less tinnitus, and better sexual functioning at 3 months and gradually disappeared. Significantly more tinnitus with 3 days as compared with 5 days in patients treated with four cycles (P = 0.0002). There were significant differences in favour of 3 cycles (vs 4 cycles) for physical (P = 0.008), role (P = 0.03), cognitive function (P = 0.04), fatigue (P = 0.003), nausea/vomiting (P = 0.008), appetite loss (P = 0.001), and overall QOL (P = 0.03) at 3 months which decreased to no difference at 1 year.
Flechtner 2016	RCT, N=382 Non-seminoma, Stage I, Germany, 1996–2005.	Mean age at study entry 31 years (Range 16–66 years)	QoL scale "overall strain (primary), QoL functioning scales: physical, emotional, social, sexual,' and global as well as symptom scales fatigue, hair loss, toxicity/symptoms (other than hair loss), and strain by toxicity/ symptoms (other than hair loss).	Group A: BEP 1 cycle, Group B: RPLND	Validated German version of EORTC QLQ-C30. Additional Questions and scales to address sexuality and overall strain by treatment and/or tumour.	Physical functioning (PF), Emotional functioning (EF), Social functioning (SF), Sexual functioning (SexF), Global QoL, Fatigue, Alopecia, Toxicity/symptoms, strain related to toxicity/ symptoms, and overall strain.	Repeated 2 monthly in first year, 3 monthly in 2nd year, 6 monthly for 3rd year until 3 years. Baseline N/R.	

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Table 1 (Continued).

Study Reference	Key Details of Study and Sample: • Study Design • Sample Size • Stage of Disease • Recruiting countries • Recruiting Period	Age at Diagnosis; Age at Survey Completion	Objectives	Interventions/ Treatment and N	PRO Measure/s Used	PRO Domains Reported	Time Points with PRO Data Reported (or Time Since Diagnosis or Treatment for Cross-Sectional Studies)	Summary of PRO Results
Fossa, Aass 1988	Cross-sectional survey. 597 TC (Data from 122 participants for long term>3 yrs post tx QOL, 64 for during treatment) Stage I–IV Norway Patients treated from 1979–1986	Range: 15–45 years	To survey the diagnosis, treatment, prognosis, and quality of life in young patients.	122 patients with long term QoL data: Group 1, Surgery: n = 29. Group 2, Radiotherapy: n= 24 Group 3, Chemotherapy + surgery: n= 43. Group 4, Chemotherapy + RT + Surgery: n = 26.	Study specific questionnaire.	Raynaud-like phenomena, GI toxicity, Peripheral sensory neuropathy, Peripheral motor neuropathy, Pulmonary toxicity, Ototoxicity, Paternity.	Cross sectional (>3 years post treatment)	Patients treated with chemo and RT has more loneliness, depression and lack of self-confidence (p, 0.05). Raynaud-like phenomena was most frequent late side effect (n=41/117 patients), was more common in cisplatin-based chemo. In general, Group 4 had more side effects than other groups. GI side effects were more common in RT group (n=5/24) which specifically included symptoms of abdominal pain, nausea and vomiting. Diarrhoea was more prevalent among participants in Group 4 (data not reported). Most patients had good self-reported health irrespective of treatment type (n=101/122).

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Fossa, de Wit 2003	RCT N=666 Seminoma and non-seminoma. Multicentre (Belgium, Netherlands, Denmark, Germany, Austria, Italy, United Kingdom, Australia, Russia). Stage II/III. 1995–1998.	Mean age at randomization 31 years (Range 16–63).	Detail analysis of HRQL related to the four treatment alternatives (BEP 3cycles vs 4 cycles, 3 days vs 5 days), with emphasis on change at 2 years.	Randomised to four groups Group 1: 3xBEP for 3 days Group 2:3xBEP for 5 days Group 3: 3x BEP +1xEP for 3 days Group 4: 3x BEP+1xEP for 5 days	EORTC QLQ-C30 and QLQ-TC26 testicular cancer module.	EORTC QLQ C 30 Functional scale - physical, role, social, emotional and cognitive. Symptoms scale- Nausea/vomiting, appetite loss, diarrhoea, constipation, pain, fatigue, sleep difficulty, dyspnoea, financial problem. QLQ-TC26 module: Specific physical symptoms-pain in hands/feet, cold hands/feet, ringing in the ears, difficulty hearing. Sexual items-sexual interest, activity, enjoyment, erectile problems, dry orgasm, sexual relationship. Emotional items-less masculinity, fertility concerns, relapse anxiety, happy with management.	Repeated measures – baseline (at randomisation before chemo), 3mon, 6mon, 1 year and 2 year.	EORTC QLQ-C30 Physical functioning: Reduced by 14 points for 4 cycle group vs 10 points for 3 cycle group (P=0.0736) at 3 months. In all groups social function decreased by >10 points at 3 months, which recovered at 6 months. Apart from nausea/vomiting and appetite loss at 3 months there were no intergroup difference in symptoms in the patterns of changes. Group 3 (4 cycles for 3 days) had more nausea/vomiting- mean score 17.3 points compared to Group 1 (3 cycles for 3 days) - mean score was 9.4. It was lowest for Group 2 (3 cycles for 5 days) - mean score 6.5. In all groups fatigue improved by approximately 4 points per year. Overall, four X 3 day cycles of chemotherapy (Group 3) resulted in the highest levels of symptoms (worst symptom burden).

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Table 1 (Continued).

Study Reference	Key Details of Study and Sample: • Study Design • Sample Size • Stage of Disease • Recruiting countries • Recruiting Period	Age at Diagnosis; Age at Survey Completion	Objectives	Interventions/ Treatment and N	PRO Measure/s Used	PRO Domains Reported	Time Points with PRO Data Reported (or Time Since Diagnosis or Treatment for Cross-Sectional Studies)	Summary of PRO Results
Fossa, Moynihan 1996	Pilot study N=206 Seminoma and non-seminoma, Stage 1 UK and Norway 1992(treatment period 1988–1992)	Median age at study 31 years (range 17–57)	To describe issues of long-term morbidity as perceived by tumour-free patients	Radiotherapy: n = 94, Chemotherapy: n==26, Surveillance: n=86	Study-specific questionnaire	Nausea/vomiting, dry ejaculation, pain/tingling hands/feet, numb/cold fingers/toes, reduced hearing/tinnitus, hair loss, tiredness/fatigue, mental depression, anxiety, reduce self-image, satisfying sexual life, worrying about fertility, satisfying partnership, fear of relapse, satisfaction with care, continuation of leisure	Cross sectional, at least 3 months post treatment.	Patients treated with radiotherapy or chemotherapy had the highest scores for neurological symptoms, Raynaud-like phenomena and ototoxicity. However, patients on surveillance also had some somatic symptoms. Peripheral parestheses, Raynaud-like phenomena and decreased hearing/tinnitus were reported by 10, 15 and 6% respectively of the patients treated by surveil lance only, and by 21, 23 and 18% of the patients in the radiotherapy group. No differences between groups on fatigue scores.

Fung 2017	Cross sectional N=952 Seminoma and non-seminoma, Stage N/R USA and Canada N/R	Median age at diagnosis 31 years (range 15–53). Median age at study 37 years (range 19–68)	To provide new information on the type and prevalence of adverse health outcomes in large numbers of cured testicular cancer patients.	Group 1, EP x 4 cycles: n=294; Group 2, BEP x 3 cycles: n=364; Group 3, BEP: x 4 cycles, n =170.	EORTC QLQ-CIPN20: scale for chemotherapy induced long term neurotoxicity.	Tinnitus, Hearing impairment, Peripheral neuropathy, Peripheral neuropathy +tinnitus +_hearing loss, Raynaud phenomenon, Peripheral vascular disease, Hypertension on drugs, Hypercholesteremia on drugs, Cardiovascular disease, Erectile dysfunction, Drugs for anxiety and depression, Self-rating of health	Cross sectional Median time since treatment 4.3 years (range 1.0 to 29.9 years)	Overall, 79.6% testicular cancer survivors (TCS) reported at least one Adverse Health Outcomes (AHO), and 20.1%, 15.0%, 10.1%, and 12.5% reported two, three, four, or five or more AHOs, respectively. Median number of AHOs after EPX4 (group 1) or BEPX3 (group 2) was two, with 34.3 and 35.1% of TCSs reporting three or more AHOs, respectively. The type and prevalence of individual AHOs after EPX4 (group 1) and BEPX3 (group 2) were similar (P. 05), except Raynaud phenomenon (11.6% v 21.4%; P, = 0.01), peripheral neuropathy (29.2% v 21.4%; P = 0.02), and obesity (25.5% v 33.0%; P = 0.04). Among all TCSs, the most common AHOs were tinnitus (37.1%), self-reported hearing impairment (31.5%), obesity (30.9%), and peripheral neuropathy (27.0%). Number of AHOs was inversely associated with self-rating of health.

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Table 1 (Continued).

Study Reference	Key Details of Study and Sample: • Study Design • Sample Size • Stage of Disease • Recruiting countries • Recruiting Period	Age at Diagnosis; Age at Survey Completion	Objectives	Interventions/ Treatment and N	PRO Measure/s Used	PRO Domains Reported	Time Points with PRO Data Reported (or Time Since Diagnosis or Treatment for Cross-Sectional Studies)	Summary of PRO Results
Glendenning 2010	Cross-sectional, N=739, UK, 1982–1992. Stage of disease not reported.	Age at diagnosis: Group 1 - No chemo:34 years (range: 15–64). Group 2- Chemo: 30 years (Range 14–58). Age at study entry: Group 1 - No chemo:44 years (range: 22–78), Group 2 - Chemo: 41 years (range 22–72).	To assess long term neurological and small vessel morbidity.	Group 1 - No chemo: N=355 (surveillance,181 and RT 174), Group 2 –Chemo: N=384 (293 chemo, 91 chemo +RT)	General health questionnaire, EORTC QLQ-C30 and testicular cancer module QLQ-TC26	Peripheral neuropathy (PN), Raynaud phenomenon (RP), Hearing loss (HL).	Ranging 9–11 yrs since treatment.	Peripheral neuropathy was more common for Group 2 – group 1 5.5% vs group 2: 12.5%; p=0.002. Reynaud's was more common for men who had chemotherapy: 1.7% vs 20.3%, P<0.001. Bleomysis dose was predictor (OR, 2.98; 95% CI, 2.286–3.883; P<0.001). Hearing: both difficulty hearing and tinnitus increased significantly with cisplatin dose despite an overall difference between chemo vs no chemo. Symptoms of hearing impairment and tinnitus persisted in >20% of patients who received platinum based chemo

Grimison 2010	Phase III RCT N=166 (149 pts for HRQL) Stage II–III Australia and NZ 1994–2000.	Median age Group A- 3 BEP: 28 years (range 14–60) Group B - 4 BEP: 32 years (range 17–62).	Overall survival, Progression free survival, QOL.	3BEP(Bleomycin 30 kU days 1, 8, and 15, etoposide 100mg/m2 days 1–5, cisplatin 20 mg/m2 days 1–5) every 21 days x3 cycles Vs 4BEP (Bleomycin 30 kU days 1, etoposide 120mg/m2 days 1–3, cisplatin 100 mg/m2 days 1) every 21 days x 4 cycles.	GLQ (Global Quality of Life Scale) 8, Utility-Based Questionnaire-Cancer.	Tiredness. Feeling sick. Feeling anxious or depressed. Numbness or pins and needles.	Baseline, At weeks 3, 6 and 9 and 12 weeks. 6, 9 and 12 months after randomisation.	The mean scores for all scales did not differ between two groups before and during treatment. At 12 weeks after randomisation the average scores for most scales were higher (side effects worse) for 4BEP. By 6 months, apart from numbness or pins and needles, others returned to baseline. At 6, 9 and 12 months, 4 BEP had higher mean scores for numbness or pins and needles (p=0.003).
Hartmann 1999	Cross-sectional, N=98 Seminoma and non-seminoma, Stage I–III. Germany Patients treated 1970 −1993.	Median age at Diagnosis 28 years (Range 17–44).	Types and incidence of sexual disturbances and fertility distress according to treatment modalities.	Group 1 - RPLND: N =13, Group 2- RT: N =4, Group 3 – Chemo: N =32 Group 4 – Chemo + RPLND: N =42 Group 5 – Surveillance: N = 7	Study specific questionnaire	Inability to ejaculate, Reduced semen volume, Dissatisfaction with sexual life, Loss of sexual drive, Reduced erectile potential.	Median 12 years (range 2.8–25.6) since diagnosis	Sexual dysfunction was experienced by45% (P=0.03) of men treated with RPLND, 55% of men treated with Chemo + RPLND (p=0.01) vs 11% in chemo. By 1–3 years, ejaculatory function recovered in 10% (3 of 29) of patients who had initial problem after treatment. No significant differences for intensity of sexual life. Loss of sexual life, reduce erectile potential and dissatisfaction with sexual life were more common among men treated with chemo+RPLND.

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Table 1 (Continued).

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Huddart 2005	Cross-sectional N=680 Seminoma and non-seminoma, Stage I–IV. UK 1997–1999.	Median age at diagnosis: – 31 years (range: 10–82). Follow-up-median age 44 years (Range: 23–78)	To understand the long-term effects of testicular cancer treatment on fertility, gonadal and sexual function	Surveillance: N=169 Chem: No=272 RT: N=158 Chemo+RT: N=81	EORTC QLQ-C30 and testicular cancer module QLQ-TC26.	Feeling less masculine, Worried about fathering children, Less interest in sex, Less sexually active, Difficulty getting erection, Sex less enjoyable, Dry ejaculation,	Cross sectional, Completed treatment 5 or more years previously	83% of the whole sample expressed satisfaction with their sexual relationship. Men who had CRT were more likely to report less interest in sex (p0.01). Men who had RT reported less sexual activity (p=0.051) and reduced sexual enjoyment (p=0.05) compared to surveillance(S). Men who had chemotherapy, as compared to men who had surveillance, reported more worries about fathering children (P=0.009).

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Joly 2002	Case-control N=71 Seminoma and non-seminoma, N=119 healthy controls Stage I–III France 1998	During study Cases (patients):– 47 years (Range 29–67) Healthy controls: 48 years (Range: 29–67)	To evaluate the influence of testicular cancer and its treatment on long-term quality of life in an unselected group of patients.	For certain analyses, comparisons were made between cases by treatment group: Surveillance: n=19, Radiotherapy: n=94, Chemotheray: n=75, Chemo+RT: n=12 RPNLD=70. Note: the main focus of the paper was cases vs healthy controls.	Short form-36 EORTC QLQ C30 Life situation questionnaire.	SF-36-Physical functioning, Role functioning–physical, Role functioning–emotional, Bodily pain, Social functioning, Mental health, Vitality, General health perceptions, Change in health, EORTC QLQ-C30 Physical functioning, Role functioning Emotional functioning, Cognitive functioning, Social functioning, Global health status, Symptoms§ Fatigue, Nausea, vomiting, Pain, Dyspnoea, Sleep disturbance, Appetite loss, Constipation, Diarrhoea, Financial difficulties, Modification of sex life	Cross-sectional. Time from treatment-Mean 11 years (range 5–20)	Scores for quality-of-life scales were similar for the three treatment groups. No relationship was observed between type of treatment and modification of sexual life. Data N/R
Jonker-Poole 1997	Retrospective study N=264 Seminoma and non-seminoma, Stage I–IV Netherlands 1977–1994	At follow-up mean age 37.7 years (range 17–71)	To evaluate changes in sexual functioning and investigate whether there is a relationship with different treatment modalities.	Surveillance=59 Radiotherapy =4 1 Polychemptherapy = 42 Chemotherapy + RRRTM: resection of residual retroperitoneal tumor mass. and=122	Study specific questionnaire with 32 items(not validated)	Libido, Arousal, Erection, Orgasm, Ejaculate, Satisfaction, Sexual Activity, Value of sexuality	Cross-sectional Mean 6.7 years follow up (range 0.25–18 years)	Surveillance had the lowest impact on sexual functioning and activity. Chemotherapy was associated with problems with libido (p=0.03), orgasm (p=0.010), ejaculation (p=0.04), and sexual activity (p=0.005) after age was adjusted for. Ejaculation problems were worse among men who had chemo +RPLND compared to men who had radiotherapy (p<0.001) or chemotherapy (p=0.002)

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Kaasa 1991	Cross-sectional N=14 Seminoma and non-seminoma, Stage I–IV Norway 1985	At treatment: mean 34 years (range 17–64 years)	Psychosocial morbidity in cured testicular cancer patients who had been in complete remission for more than 3 years.	Patients divided into four groups as per treatment 1.Surgery: n = 32, 2. Radiotherapy: n = 39, 3.Chemotherapy + surgery: n = 46, 4.Chemotherpay + radiotherapy + surgery: n = 32,	Non-validated questionnaire	Working ability - Physical exhaustion, Concentration and Attention, Comfortable with work, Medication/sleeping Problems, Use of pain medication, Use of tranquilisers, Sleeping problems, Social support, Support, Loneliness, Health and well-being, Health, Satisfied/dissatisfied, Strong and fit/tired, worn out.	Cross sectional. Mean time since treatment 5.1 years (range 3–9)	There were no differences between the treatment groups for working ability, use of analgesics, and sleeping problems. There was a tendency for the patients in subgroup 4 to use tranquilisers more frequently along with tendency to worse health (P = 0.09), to be less satisfied with life in general (P = 0.12) and to feel less strong and fit (P = 0.06). There was a slightly higher incidence of depression in subgroup 4 (65%) compared with the others (3.5, 31% and 37%, respectively) (P = 0.08).

Kerns 2018	Cross-sectional N=1214 Seminoma and non-seminoma, N/R North America Recruitment period not reported.	Median age at diagnosis – 30 years (range: 15–60). Mean age at evaluation- 37 years (range 18–74).	To provide new information about cumulative burden of morbidity after contemporary cisplatin-based chemotherapy.	BEP: n=710 EP: n=388 VIP: n=44 Other: n =69	Questionnaire not reported.	Peripheral sensory neuropathy, Autonomic neuropathy, Hearing damage, Tinnitus, Raynaud phenomenon, Pain, Anxiety and/or depression, Erectile dysfunction, Hypogonadism, other health conditions	Cross sectional. Median time since completion of chemotherapy: 4.2 years (range 1–30)	BEPx4 (OR, 1.44 v BEPx3), VIP x 4 (OR, 1.96 v BEP x 3) were associated with higher cumulative burden of morbidity (CBM) in a multivariable model. No significant differences were observed for individual adverse health outcomes except Raynaud phenomenon (P,0.001), for which prevalence and severity after BEP x3 (183 [39.8%]:18.5% grade 1, 10.4% grade 2, 10.9% grade 3) exceeded EP x 4 (84 [23.8%]: 12.2% grade 1, 16.8% grade 2, 4.8% grade 3). Other AHOs were almost similar.
Kim 2011	Case-control N=246 Seminoma and non-seminoma, N=236 healthy controls USA 2002–2005	Mean age not reported.	To address the gap of knowledge in quality of life for testicular cancer survivors in the United States by treatment type and individual components of QoL.	Radiotherapy: n=100 Chemotherapy: n =75 Surgery: n=241	SF-36	Physical functioning, role–physical, bodily pain, general health, vitality, social functioning, role–emotional, and mental health perceptions.	Cross-sectional. For cases, the median time between diagnosis and interview was 14 years (mean = 13.7 years). All cases were diagnosed at least 5 years prior to interview.	Chemotherapy group had lowest SF-36 PCS (physical component score) (P=0.0032) and mental component score (MCS) (p=0.039). Chemotherapy group had low physical functioning (p=0.027), role-physical (p=0.0044), general health (p=0.0001), vitality (p=0.011), social functioning (p=0.016) and mental health (p=0.028) compared to other types of treatment.

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Miyake 2004	Cross-sectional, N=102 patients (Group A = 38, Group B =24, Group C = 40) diagnosed with seminoma or non-seminoma, who had not shown any evidence of disease for at least 6 months. Japan.	Overall mean age 35.6 years at orchiectomy. Age at time of survey N/R	To evaluate the HRQoL in patients with germ cell tumours who received standard-dose chemotherapy or high-dose chemotherapy combined with peripheral blood stem cell transplantation, and to compare the HRQoL of these patients with patients who had undergone surveillance therapy only.	Group A: standard-dose chemotherapy (cisplatin-based combination) Group B: high-dose chemotherapy combined with peripheral blood stem cell transplantation, following standard dose chemotherapy, Group C: surveillance monitoring	SF-36 survey (version 1.20)	physical functioning (PF), role-physical functioning (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role-emotional functioning (RE) and mental health (MH).	One cross-sectional assessment. Mean time since orchiectomy (months_ Group A: Mean 26.5 ± 9.3 months. Group B: mean 21.5 ± 8.8months. Group C: 51.3 ±16.9 months	Mean ±SD In patients undergoing chemotherapy (groups A and B), PF 78.2 ± 13.5, RP 68.1 ± 35.2, BP 72.8 ± 23.9, GH 61.2 ± 7.7, VT 72.2 ± 10.6, SF 46.9 ± 8.0, RE 66.8 ± 30.7, MH 66.9 ± 13.3. Group C(surveillance) PF 82.2 ± 13.8, RP 61.8 ± 33.9, BP 81.3 ± 22.4, GH 58.1 ± 14.7, VT 74.2 ± 16.6, RE 50.8 ± 10.3, SF 69.7 ± 41.6 MH 67.1 ± 18.2, No significant differences were observed in any SF-36 scale scores between patients with and without chemotherapy (ie groups A and B Vs Group C).

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Mykletun 2005	Cross-sectional N=1409 Stage I–III Norway 1998	Overall mean age 45 years (SD 10.2) at the time of study	Long-term QOL in relation to treatment modality, side effects, and TC-related stress.	Surveillance: n= 117, RPLND: n= 151, RT: n=598, Chemo+_RPLND/RT: n=543.	SF-36, The impact of event scale (IES), The brief male sexual function inventory (MNSFI)	PF physical functioning; RP, role physical; BP, bodily pain; GH, general health; VT, vitality; SF, social functioning; RE, role emotional; MH, mental health; PCS, Physical Composite Score; MCS, Mental Composite Score.	Mean time of survey since orchiectomy was 11 years (SD 4.2)	Mean difference of 1.3 points for physical component score was found between chemo and surveillance groups. After adjustment for age, no statistical effects of treatment on PCS and MCS were found. Chemotherapy group had more severe peripheral neuropathy and Raynaud's (OR=3.8), And a higher rate of two or more side effects (OR=3.0).
Oechsle 2016	Cross-sectional N=164 Stage I–III Germany 2012	Mean age at survey 44.4 years (SD 9.6)	Primary aim: examine the level of symptom burden in long-term survivors. Secondary aim: to examine the impact of socio-demographic and disease and treatment-related characteristics on symptom burden.	Surgery: n=160 RT: n= 37 Chemotherapy: n=114	Memorial Symptom Assessment Scale–Short Form (MSAS-SF).	Lack of energy, feeling drowsy, difficulty sleeping, difficulty concentrating, sweets, numbness and tingling, pain, reduced sexual inters, itching, cough, SOB, dizziness, mouth sores, hair loss, diarrhoea, skin changes, mucositis, nausea, feeling bloated, food taste, lack of appetite, problems with urination, constipation, swelling of arms/legs, difficulty swallowing, do not look like self, weight loss, vomiting.	Cross-sectional study at a mean of 11.6 years (SD 7.3) since diagnosis	There were no significant bivariate or multivariate associations between symptom burden and characteristics of primary tumour presentation (Including limited versus metastatic disease), first-line treatment, tumour relapse, or overall treatment (data N/R). Multivariate analysis was same as bivariate association.

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Oldenburg 2006	Cross-sectional N=684 I–III Norway Stage: 1998–2001	Mean age at survey: 45.1 years (SD 10.7) Mean age at diagnosis: 33.7 years (SD 10.2)	To assess the internal consistency, reliability and the factor structure of SCIN (scale of chemotherapy induced neurotoxicity). Also test internal and external validity of the SCIN.	Surgery (Orchiectomy +_RPLND): n=146, Radiotherapy: n=300, Chemotherapy: n=238.	Scale for chemotherapy inducing long-term neurotoxicity (SCIN)	Peripheral sensory neuropathy (paraesthesia), Raynaud's phenomenon, ototoxicity.	Cross-sectional at a mean of 11.4 years (SD 4.3) since diagnosis	In the surgery and radiotherapy Groups, 59–77% of the sample reported none of the 6 possible symptoms, while this was the case for 50–60% of men in the chemotherapy group. There were no significant differences between the surgery and radiotherapy group except of a higher proportion of patients with "pain, paresthesias in the feet/ toes", reported by irradiated patients. Of note, 30 (10%) of the radiotherapy group reported "very much" on either item 3a (Tinnitus) or 3b (Impaired hearing). In a sub-group analysis, the proportion with high SCIN scores (4–6) was 28–37% in the low-dose chemotherapy group, and 63–72% in the high-dose chemotherapy group. Conversely, low scores (0–3) were found in 53–54% and in 46–47% of men in the low-dose and high-dose group, respectively. For all three subscales these differences reached the level of statistical significance.

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Oldenburg 2007	Crossectional cohort N=238 Stage I–IV Norway	Diagnosis: (median) 29 years, range 15–64 years; Participation (median): 42.3 (22.7–73.4)	To assess the impact of polymorphisms in Glutathione S-transferase (GST) -P1, - M1, and -T1 on self-reported chemotherapy-induced long-term toxicities in testicular cancer survivors (TCSs).	Cisplatin-based chemotherapies: Cisplatin (n = 238): 397 (81–1571) Bleomycin (n = 226): 145 (29–212) Vinblastine (n = 105): 35 (10–51) Etoposide (n = 146): 1434 (41–4934)	Scale for Chemotherapy-Induced Neurotoxicity (SCIN) by Fossa et al, which covers six symptoms (items), and EORTC QLQ-C30	Paraesthesia, Raynaud-like phenomena, ototoxicity	Median 12 years (range: 4–19 years) after diagnosis	Cumulative doses of cisplatin and age at survey were positively associated with SCIN-total-score: OR 1.35 (1.06–1.71), p=0.014. Cumulative dose of cisplatin was significantly associated with paraesthesia in the toes p<0.001, Raynaud-like phenomena in the toes p<0.001 and with both tinnitus p0.001 and hearing impairment p <0.001. The risk of a more severe symptom class increased by roughly 1.3 for each step of 100 mg/m2 cumulative cisplatin, the dose corresponding to one cycle of chemotherapy.

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Oliver 1994	Prospective Observational Study. UK N=224 Patients diagnosed between 1982 and 1992	At diagnosis: not stated At survey completion (median): Surveillance group: 36 years. Radiotherapy group: 34 years. Chemotherapy group: 36 years.	Primary: To evaluate the efficacy of surveillance, prophylactic radiotherapy, and adjuvant chemotherapy, and discuss these differing management approaches.	Group A: Prophylactic radiotherapy: N=79 Group B: Surveillance alone: N=67 Group C: adjuvant single agent platinum: N=78 (C.1. Received two courses of platinum: n=53; C.2. Received one course of platinum: n=25)	Unclear	Physical symptoms Immediate side effects: Sickness & Diarrhoea Late side effects: Fertility & Indigestion problems	Cross-sectional, ranging from 6–118 months follow up.	Radiotherapy group had higher rates of diarrhoea than all other groups. More acute nausea and vomiting in the patients receiving two courses of adjuvant chemotherapy. Most of these were treated before the availability of 5-HTs antagonist antiemetics.Relative to surveillance patients, there was some delay in return to work in patients receiving either radiotherapy or two courses of chemotherapy though preliminary results suggest one course was better tolerated and there was an earlier return to work.Sickness Group A: 36% Group B: 6% Group C.1: 25% Group C.2: 50% Diarrhoea Group A: 60% Group B: 4% Group C.1: 0% Group C.2: 12% Indigestion problems Group A: 30% Group B: 11%Group B: 6% Group C.1: na Group C.2: 6%

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Rossen 2009	Cross-sectional study Denmark N=401 Stage of disease not reported	Age at diagnosis not reported. Age at survey completion: A= surveillance group (48.9) B= radiotherapy group (48.8) C= chemotherapy group (44.5)	To examine QOL, depression, physical symptoms, and fatigue among a large, representative, and consecutive sample of Danish testicular cancer survivors.	On the basis of their treatment, participants were categorized as having received surveillance, radiotherapy, or chemotherapy.	EORTC QLQ-C30, Beck Depression Inventory-II (data not extracted here), Multidimensional Fatigue Inventory-20, and study-specific questions for neurotoxic symptoms and Raynaud-like phenomena.	Physical, cognitive, emotional, and social roles, financial impact, fatigue, pain, and nausea and vomiting, global health,dyspnoea, loss of appetite, insomnia, constipation, and diarrhoea. General fatigue, Physical fatigue, Reduced activity, Reduced motivation, Mental fatigue	Cross-sectional – patients eligible if they had completed treatment more than 3 years prior. Mean follow-up time was 12.2 years (SD 3.07).	No statistically significant differences were found between treatment groups on the QLQ-C30 or MFI-20 subscales. Chemotherapy patients reported highest levels of neurotoxic symptoms and Raynaud-like phenomena, which was statistically higher compared with surveillance patients ($p<0.001$) but not radiotherapy patients.
Rudberg 2000	Cross-sectional study Sweden N=277 patients Disease stage not specified.	Mean age at diagnosis 34.4 years (SD 11.4). Mean age at survey completion: 42.2 years, (SD = 12).	To investigate long-term health-related quality of life among TC survivors	Adjuvant radiotherapy: N= 102 (37.1%). Retroperitoneal lymph node dissection (RPLND) plus chemotherapy: n = 77 (27.8%). RPLND: n= 33 (11.9%). Chemotherapy: n= 28 (9.8%). Surveillance only:n= 22 (8.0%). Radiotherapy plus chemotherapy (with or without RPLND): n= 15 (5.4%). All had Orchiectomy.	The Swedish Health-Related Quality of Life Questionnaire (SWEDQUAL); a study-specific questionnaire with 18 questions on testicular cancer; and The Gothenburg Quality of Life Instrument.	(1) physical functioning, (2) mobility, (3) satisfaction with physical health, (4) role limitations due to physical health, (5) pain, (6) positive affect, (7) negative affect, (8) role limitations due to emotional health, (9) sleep problems, (10) satisfaction with family life, (11) marital functioning, (12) sexual functioning, (13) general health perceptions. Perceived attractiveness	Cross-sectional: mean 7.8 years post treatment.	Men who had undergone RPLND plus chemotherapy reported significantly more pain ($F[5,268] = 2.39$, $p < 0.05$), whereas men who had undergone radiotherapy plus chemotherapy with or without RPLND reported less satisfaction with family life and poorer sexual functioning compared with the other treatment groups ($F[5,244] = 2.44$, $p < 0.05$, and $F[5,252] = 3.3$, $p < 0.01$, respectively). Men treated with chemotherapy, either as a single therapy or in combination with other treatments, scored less favourably regarding quality of life.

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Rudberg 2002	Cross-sectional study Sweden N=277 Disease stage not specified.	Mean age at diagnosis 34.4 years. Mean age at survey completion: 42.2 years	1. To delineate and compare frequency of self-perceived physical, psychologic, and general symptoms in men treated for testicular cancer with those of a general population. 2. To compare self-perceived physical, psychologic, and general symptoms in relation to secondary Raynaud phenomena, sexual dysfunction, infertility, and self-perceived attractiveness in different treatment modalities.	Adjuvant radiotherapy: N= 102 (37.1%). Retroperitoneal lymph node dissection (RPLND) plus chemotherapy: n = 77 (27.8%). RPLND: n= 33 (11.9%). Chemotherapy: n= 28 (9.8%). Surveillance only:n= 22 (8.0%). Radiotherapy plus chemotherapy (with or without RPLND): n= 15 (5.4%). All had Orchiectomy.	The Swedish Health-Related Quality of Life Questionnaire (SWEDQUAL); a questionnaire consisting of 18 specific questions or statements concerning the testicular cancer; and The Gothenburg Quality of Life Instrument.	Self-perceived symptoms among 7 categories: depression, tension, gastrointestinal and urinary, musculoskeletal, metabolic, cardiopulmonary, and head. Also, Raynaud Phenomena, infertility, sexual function, and self-perceived attractiveness.	Cross-sectional: mean 7.8 years post treatment.	Those treated with CT either as a single therapy or in combination with other treatment modalities reported cold white fingers more often than the other treatment groups ($X2 = 17.5$; $df = 5$; $P = 0.004$) as well as numbness in feet/toes $X2 = 14.75$; $df = 5$; $p = 0.01$).The men who had undergone the treatment regimen of RT plus CT and/or RPLND scored significantly lower in sexual interest ($F = 2.88$; $df = 5$; $P = 0.01$) and in the ability to enjoy sex ($F = 2.56$; $df = 5$; $P = 0.02$) compared with all the other treatment groups. They also reported significantly more erectile difficulties ($F = 3.2$; $df = 5$; $P = 0.006$).

Schmidt 2018	Retrospective case-control study. N=127. Stage II,III disease. Denmark 2015 (treated between 1993–2013).	Median age at diagnosis 27.1 years (range: 15.3–64.4 years)	To evaluate oncological results, survival, complications and the impact of conservative surgical procedure on quality of life (QOL) and working ability with a long (up to 20 years) follow-up.	Cases- Radical resection after chemo for any residual mass >-10mm: n=67. Controls – chemotherapy without surgery (no retroperitoneal limited resection for residual tumour mass): n=60. All participants had orchiectomy	EORTC – QLQ C-30	Physical functioning, role functioning, cognitive functioning, emotional functioning, social functioning, fatigue, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea, financial difficulties, nausea and vomiting and global health/QOL	Cross-sectional, median 124 months follow up (range: 10–377 months)	Mean score (95% CI) of operated patients vs controls (chemotherapy without additional surgery): Global health status 76 (71–82) vs 74 (69–80) p= 0.44, Physical functioning 93 (89–97) vs 96 (94–99) p = 0.46, Role functioning 88 (82–94) vs 94 (90–97) p=0.56, Emotional functioning 85 (80–90) vs 89 (85–92) p=0.80, Cognitive functioning 86 (81–91) vs 84 (79–89) p=0.42, Social functioning 90 (85–96) vs 92 (88–96) p=0.52, Fatigue 19 (12–26) vs 17 (12–22) p=0.49, Nausea and vomiting 4 (1–8) vs 1 (0–1) p=0.04, Pain 10 (5–16) vs 9 (5–13) p=0.48, Dyspnoea 10 (4–15) vs 9 (5–14) p=0.49, Insomnia 15 (9–22) vs 16 (10–22) p=0.40, Appetite loss 5 (1–9) vs 4 (1–8) p=0.91, Constipation 5 (1–9) vs 3 (0–6) p=0.86, Diarrhoea 7 (3–12) vs 5 (2–8) p=0.59, Financial difficulties 12 (5–19) vs 8 (2–14) p=0.47. Nausea and vomiting was statistically significantly higher for the operated patients as compared to controls (p=0.04), however the absolute difference in scores was less than 10 points, so it was not clinically significant.

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Skaali, Fossa, Anderson 2011	Cohort study Norway N=122 Disease Stage I = 88 (72); Stage II to IV = 34 (28)	Age at diagnosis not reported. Median age at baseline survey completion: 32.5 years (range: 19–60)	Primary: to compare the proportions of TCPs with an increase of self-reported cognitive problems from baseline to 1-year follow-up among patients treated with different treatment modalities (no chemotherapy, one cycle of chemotherapy, or multiple cycles of chemotherapy). QOL endpoint: to study variables associated with an increase of self-reported cognitive problems from baseline to 1-year follow-up, including	NO-CHEMO group: n=31 ONE-CHEMO group (one cycle of chemo): n=38 MULTIPLE-CHEMO group (2 or more cycles of chemo): n=53 The chemotherapy regimens consisted of one treatment with carboplatin or of cycle(s) with bleomycin, etoposide, and cisplatin (BEP chemotherapy).	The Impact of Event Scale (IES), The Fatigue Questionnaire, Scale for Chemotherapy-Induced Neurotoxicity (SCIN)	Most PROs were reported as one score or percentages at different time points, and the SCIN assessment reported: Peripheral neuropathy Raynaud-like symptoms Tinnitus or hearing loss	Baseline: after orchiectomy, but before any further treatment like chemotherapy. Follow-up: 1 year post-treatment	There was a significant (P=0.02) difference across the treatment groups in proportions of TCPs with an increase of self-reported cognitive problems: larger proportions in the ONE-CHEMO group (29%) and the MULTIPLE-CHEMO group (25%) had an increase in problems compared to the NO-CHEMO group (3%). However, no significant difference appeared between the ONE- and the MULTIPLECHEMO group (P=0.64).

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Skaali, Fossa, Dahl 2011	Pooled PRO analysis of patients from 3 RCTs N = 347 Stages I–4 Norway	Mean age at Baseline: Chemo group: 33.0 years (SD 8.8) Radiation group: 38.2 years (SD 8.0)	To explore cognitive complaints in patients with testicular cancer treated with chemotherapy or radiotherapy during the 1990s	1. Chemotherapy (CHEM) group may have included: bleomycin, etoposide, and cisplatin (BEP) chemotherapy (3 or 4 cycles given over 3 or 5 days). 2. Radiotherapy group (RAD) consisted of irradiated patients given 20 Gy vs 30 Gy abdominal radiotherapy	EORTC QLQ-C30	Cognitive functioning, Emotional functioning, role functioning, Social functioning, fatigue, insomnia, neurotoxic	Baseline 3 months and 12 months	Significantly more patients in the CHEM group had concentration problems at 3 months compared with baseline and 12 months. Also the proportion of patients with concentration problems at 3 months was significantly higher in the CHEM group than in the RAD group. In contrast, the proportions with concentration problems at baseline and 12-month follow-up did not significantly differ between the CHEM and the RAD groups. The proportion with cognitive function problems in the CHEM group at 3 months was significantly higher compared with the proportions at baseline and 12 months. At 3 months, the CHEM group also had a significantly higher proportion of patients with cognitive function problems than the RAD group. At 3 months, the CHEM group had a higher proportion of emotional functioning (n=103 (37%) VS n=12 (12%)), role functioning (n=178 (65%) VS n=15 (21%)) and social functioning (n=144 (52%) VS n=15 (21%)) issues compared to the RAD group, respectively.

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Table 1 (Continued).

Study Reference	Key Details of Study and Sample: • Study Design • Sample Size • Stage of Disease • Recruiting countries • Recruiting Period	Age at Diagnosis; Age at Survey Completion	Objectives	Interventions/ Treatment and N	PRO Measure/s Used	PRO Domains Reported	Time Points with PRO Data Reported (or Time Since Diagnosis or Treatment for Cross-Sectional Studies)	Summary of PRO Results
Skallenberg 2020	Longitudinal Cohort N=82 Stages 1–4 Norway	Age at S3 survey: median 61 years (range 46–83 years).	The present exploratory study provides a longitudinal analysis of Cisplatin-based chemotherapy -related HL in TCSs 3 decades after their Cisplatin-based chemotherapy, based on audiograms, speech audiometry, and patient-reported hearing.	Cisplatin-based chemotherapy	The validated Scale for Chemotherapy-Induced Neurotoxicity (SCIN)	Hearing loss	Median 31 years (Range: 22–37 Years since diagnosis at this survey)	Subjective hearing loss was reported by seven patients (9%) in S1 and by 20 patients (26%) in S3. Age-adjusted hearing loss at S1: 7/7, at S3: 13/20 (65%) had age-adjusted hearing loss (ie worse than their age in general population). Higher cisplatin dose, as compared with standard dose, was significantly associated with higher age-adjusted thresholds at 4, 6, and 8 kHz at both S1 and S3, but no comparisons on hearing loss by cisplatin dose were performed.

Skoogh 2012	Cohort N=960 Stage 1–4 Sweden	Age at survey: mean 30 years, range: 16–64 years	The objective was to study self-reported behaviours that may depend on cognitive function, among testicular-cancer survivors who received various cycles of cisplatin-based chemotherapy by comparing them with those who did not.	Participants were grouped according to whether they had: 0 cycles of chemotherapy 1–2 cycles 3–4 cycles 5 or more cycles. Participants had different variations: Cisplatin Etoposide Bleomycin IE; Vinblastine Ifosfamide. Some also had Retroperitoneal lymph node dissection (self-reported) Radiotherapy (self-reported)	Study specific questions on language, fatigue, sexual design and hearing, in addition to HADS (not extracted)	Fatigue Sexual desire Hearing	Mean 11, range 3–26 years since diagnosis	Men who had 5 or more cycles of chemotherapy were at increased risk of language difficulties as compared to all other groups. Specifically, saying similar but wrong words: 3.3 (1.5–7.2), p= 0.0011; difficulties understanding meaning: RR 3.2 (1.3–7.8), p= 0.0079; words coming out in wrong order: 3.1 (1.7–5.9), p=0.002, saying other words than planned: 2.3 (1.1–4.6), p=0.01; difficulties completing sentences: 2.0 (1.0–3.7), p=0.02. Findings were similar when adjusted for education level. The percentage of men who experienced hearing or fatigue issues was similar across all groups.
Sprauten 2012	Cohort study Norway N=169 Stage of disease (Royal Marsden stage): I - 29 (17) IM - 5 (3%) II - 79 (46) III - 10 (6) IV - 46 (27)	Median age at diagnosis: 28.7 years. Median Age at survey completion: Survey 1 = 40 years, Survey 2 = 50 years.	To examine the association between long-term total serum platinum and the prevalence or severity of peripheral paresthesias, Raynaud's phenomenon, and ototoxicity in a well-characterized cohort of TCSs, taking into account cumulative cisplatin dose, time since treatment, and other variables. QOL objective not clearly defined.	All had orchidectomy and received chemotherapy: Vinblastine (CVB). (40.8%), standard bleomycin and either etoposide (BEP) (39.1%) and other dose-intensive regimes (18.3%).	Scale for Chemotherapy-Induced Neurotoxicity (SCIN)	Neuropathy in hands (fingers) and feet (toes), Raynaud's phenomenon in hands (fingers) and feet (toes), tinnitus, and impaired hearing.	Timepoint 1: national FU survey conducted throughout 4 years, approx. 12 years post-treatment. Timepoint 2: Questionnaire-based Survey II (2007) was performed a median 8 years (range, 7 to 9 years) after Survey I, hence approx. 20 years post-treatment.	There were no statistical differences in symptom severity between men who received the CVB or the BEP regimen as their initial treatment. Total SCIN score was positively associated with administered cisplatin dose, dose-intensive therapy, and age at survey (p=0.016, P=0 0.032, and P=0.035, respectively). These variables were included in multivariate analyses for both surveys. Multivariate analyses. Cumulative dose of cisplatin was not associated with either total SCIN score (OR, 1.10; 95% CI, 0.88 to 1.39) or any of the individual symptoms

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Table 1 (Continued).

Study Reference	Key Details of Study and Sample: • Study Design • Sample Size • Stage of Disease • Recruiting countries • Recruiting Period	Age at Diagnosis; Age at Survey Completion	Objectives	Interventions/ Treatment and N	PRO Measure/s Used	PRO Domains Reported	Time Points with PRO Data Reported (or Time Since Diagnosis or Treatment for Cross-Sectional Studies)	Summary of PRO Results
Vidrine 2010	Cohort study The United States and Netherlands, 2 centres. N=116. Stage N/R.	Mean age at survey completion: 31 years for the US group, and 27.9 years for the Netherlands group	To compare HRQOL outcomes between men who received a treatment regimen consisting of orchiectomy and surveillance with men who received orchiectomy plus adjuvant chemotherapy.	Surveillance 27 (24%) Adjuvant chemotherapy 89 (76%)	The 36-Item Short-Form Health Survey (SF-36)	Bodily pain Role physical Social functioning General health Mental health Physical health Role emotional Vitality	Participants completed assessments approx. 1 week after the completion of adjuvant chemotherapy, (or 3 months after baseline for those who did not receive adjuvant chemotherapy) and 12 months after the baseline assessment.	Findings indicated that men treated with chemotherapy reported significantly more bodily pain, poorer role physical functioning, poorer social functioning, poorer physical health, more fatigue compared with the men who did not receive chemotherapy at the post-treatment assessment. At the time of 12 month follow-up, HRQOL scores did not vary by treatment group, and scores were significantly higher than baseline HRQOL scores. No significant time by treatment group interactions were observed at the 12 month follow-up.

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Whitford 2019	Prospective cohort study. Australia and New Zealand, 16 centres. N=145. Stage of disease not stated	Age at diagnosis not reported. Age at survey completion: 34.8 for the chemotherapy groups, and 34.5 for the surgery only group	the primary endpoints were six objective cognitive tasks measured using coghealth: psychomotor function, visual attention/vigilance, complex decision making, visual attention, visual learning, and working memory. qol objective: secondary endpoints included the assessment of psychological variables known to impact cognitive function, including quality of life (qol) which was assessed over time, between groups, and controlled in primary and secondary analyses.	Group A -surgery + chemotherapy (etoposide and cisplatin ± bleomycin, BEP/EP; or single agent carboplatin): n=61, Group B surgery alone: n=41.	The Functional Assessment of Chronic Illness Therapy-Fatigue (FACT-F) - 41-item scale	Emotional well-being Functional well-being Physical well-being Social/family well-being Fatigue	Repeated measures. Two assessments: one at baseline (≤ 6 months post-orchiectomy/pre-chemotherapy), and a follow-up (12–18 months post-baseline). PRO data reported by each domain. See PRO score per domain column	Groups showed no differences in subjective cognitive dysfunction. The chemotherapy group showed higher anxiety, poorer functional well-being and worse fatigue compared to the surgery-only group at < 6 months post-surgery/pre-chemotherapy) but not 12–18 months later. For both groups, emotional well-being, functional well-being and anxiety significantly improved over time. Mean (SD) Emotional well-being Baseline: A = (n=61) 18.88 (4.05); B = (n=41) 20.52 (2.97) FU: A = (n=59) 21.15 (2.47); B = (n=39) 21.18 (3.09) Functional well-being Baseline: A = (n=61) 21.31 (5.50); B = (n=41) 23.63 (4.62) FU: A = (n=59) 24.36 (4.00); B = (n=39) 24.93 (3.62) Physical well-being Baseline: A = (n=61) 23.62 (4.23); B = (n=41) 25.83 (2.50) FU: A = (n=59) 26.21 (2.01); B = (n=40) 26.55 (2.17) Social/family well-being Baseline: A = (n=61) 24.31 (4.09); B = (n=41) 23.69 (4.65) FU: A = (n=59) 24.38 (4.24); B = (n=40) 23.88 (4.39) Fatigue Baseline: A = (n=61) 41.93 (1.04); B= (n=41) 45.24 (1.27) FU: A = (n=59) 44.60 (1.06); B = (n=40) 47.23 (1.28)

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Table 1 (Continued).

Study Reference	Key Details of Study and Sample: • Study Design • Sample Size • Stage of Disease • Recruiting countries • Recruiting Period	Age at Diagnosis; Age at Survey Completion	Objectives	Interventions/ Treatment and N	PRO Measure/s Used	PRO Domains Reported	Time Points with PRO Data Reported (or Time Since Diagnosis or Treatment for Cross-Sectional Studies)	Summary of PRO Results
Studies Not Including Chemotherapy Intervention								
Caffo 2001	Cross-sectional N=98 Seminoma Italy Stage I disease	Median age at time of treatment: 36 years (Range: 21–68 years). Median age at time of questionnaire 48 years (Range: 26–85 years)	The main purpose of our report is to provide a QL evaluation of a monoinstitutional series of Italian patients treated with radiotherapy alone after orchiectomy for early-stage testicular cancer.	Radiotherapy (radiation techniques varied because patients were treated over a span of 35 years.	Study-specific QOL questionnaire	Physical wellbeing Psychological wellbeing Autonomy Relationship life Sexual life Intestinal functioning General items	Median time since therapy was 123 months (range, 15–432 months).	63 and 73.5% judged their health status and their quality of life as good or very good, respectively. N=3/96 patients noted some blood in the urine or had some difficulties in controlling urination. The urinary score was above the central point in 99% of the patients. Diarrhoea was reported at a high grade by four patients (4%), while three patients (3%) reported a low grade of blood in the stools. Twenty-three patients (23%) reported a low degree of libido, and13 (13%) defined their sexual capacity as poor. The ability of having an erection was considered satisfactory by 70 patients (71%), although 74 patients (75%) reported an erection sufficient for sexual intercourse. A frequent nocturnal penile tumescence was reported by 23 patients (23%). Seventy-two patients (73%) reported a good capacity to achieve orgasm. Sexuality was considered as a significant problem by 11 patients (11%).

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Gamuliin 2011	Cohort study, N= 115, Seminoma, Stage I, Croatia, 2011	Average age at diagnosis= 34 years (Range:19 to 72 years)	To establish the side effects during and after radiotherapy.	RT of the para-aortic lymph node after orchidectomy	EORTC QLQ-C30, RTOG (Radiation Therapy Oncology Group) – recommended toxicity criteria.	Nausea, diarrhoea, vomiting, fatigue, nausea and vomiting, nausea and hard stool, nausea and diarrhoea, nausea, vomiting and diarrhoea, nausea and fatigue, anorexia with weight loss, sleep problems, worried and anxious, breathing problems, stomach pains, social problems, physical condition, quality of life.	Immediately after RT and 13 to 84 months after RT (median 28 months)	Symptoms during and after radiotherapy. Nausea: 25% Diarrhoea: 2% Vomiting: 1%, Fatigue: 4%, Nausea and vomiting: 15%, Nausea and hard stool: 8%, Nausea and diarrhoea: 7%, Nausea, vomiting and diarrhoea: 4%, Nausea and fatigue: 27%, Anorexia with weight loss: 51%, Sleep problems: 12%, Worried and anxious: 35%, Breathing problems: 4%, Stomach pains: 16%, Social problems:23%, QOL in the last week of RT Poor, very poor: 14%, Medium: 20% Good/excellent: 66%
Jones 2005	RCT N= 625 Seminoma Stage I United Kingdom, the Netherlands, Italy, Norway, Belgium, Australia, and New Zealand. 1995 to 1998	Median age: 38 years (range 20–80 years)	To assess the possibility of reducing radiotherapy doses without compromising efficacy in the management of patients with stage I seminoma.	Group 1: Radiotherapy 30 Gy for 15 fractions (n = 313), Group 2: Radiotherapy 20 Gy for 10 fractions (n = 312)	Diary card non-validated) of symptoms	Lethargy, work status, nausea or vomiting, diarrhoea, and medication for symptoms. Symptoms were recorded as none, mild, moderate, or severe, with the number of vomits and bowel openings also recorded.	The median time from orchidectomy to the start of treatment was approximately 7 weeks. Diary completed daily for 4 weeks from the start of treatment and then weekly for the next 8 weeks.	Four weeks after starting radiotherapy, significantly more patients receiving 30 Gy reported moderate or severe lethargy (20% v 5%) and an inability to carry out their normal work (46% v 28%). However, by 12 weeks, levels in both groups were similar.

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Table 1 (Continued).

Study Reference	Key Details of Study and Sample: • Study Design • Sample Size • Stage of Disease • Recruiting countries • Recruiting Period	Age at Diagnosis; Age at Survey Completion	Objectives	Interventions/ Treatment and N	PRO Measure/s Used	PRO Domains Reported	Time Points with PRO Data Reported (or Time Since Diagnosis or Treatment for Cross-Sectional Studies)	Summary of PRO Results
Wortel 2015	Longitudinal study N=161/238 patients returned questionnaires. Stage I–ii testicular seminoma The Netherlands	Age at treatment: Median 36yrs, range 18–70 years Age at survey completion N/R	The aim of the current study was to prospectively evaluate short-term effects of orchiectomy followed by radiotherapy on body image and sexual function in testicular seminoma patients.	Prophylactic or adjuvant radiotherapy after orchiectomy.	Three study specific questionnaires assessing incidence and severity of orchiectomy and radiotherapy on body image and sexual function.	Effects of orchiectomy and radiotherapy on body image and Sexual interest, activity, pleasure, function, and satisfaction.	After orchiectomy but before radiotherapy, 3 months and 6 months post radiotherapy.	After orchiectomy, 51% reported minor changes in body image due to their missing testicle, while 10% reported moderate to severe changes. 0/14 patients with a testicular prosthesis reported changes in body image, problems during sexual activity or problems with undressing in the presence of others. **Post orchiectomy VS 6 months post radiotherapy**: Sexual interest in past 4 weeks: no difference (P=0.07) Difficulty maintaining erections: no difference (p=0.08) Quality of spontaneous erections: no difference (p=0.88) Quality of erections: significantly decreased at 6 months post RT: p=0.016

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Poulakis 2006	Case control study. N=50 Stage I Germany 2001	L-RPLN: Mean 29 years (SD: 3.5), O-RPLN: mean 31 years (SD 4.5). All patients had surgery within the past three years.	To compare the postoperative recovery and QoL in laparoscopic (L) vs open (O) RPLND in stage I non seminoma.	Laparoscopic -RPLND: n=21, Open-RPLND: n=29.	SF-36, EORTC QLQ-C30	SF-36:Physical functioning, social functioning, Roles physical restrictions, bodily pain, general health, vitality. EORTC QLQ-C30: physical, role, emotional and social functioning, Global QOL, fatigue, pain	Pre-operative, 1, 3 and 6 months post-operative.	Laparoscopic group had better outcomes in all domains (both SF 36 and EORTC QLQ –C30) at 1, 3 and 6 months vs Open group ($p<0.05$). Laparoscopic group returned to normal general activities earlier; The mean post-operative time to return to baseline QOL score was 28.8 days (SD 14.1) in Laparoscopic vs 50.5 days (SD 17.1) in the Open group ($p<0.001$).

Notes: N/R, not reported; N/A,not applicable; RPLND, retroperitoneal Lymph node dissection; RT, radiotherapy; BEP, bleomycin, etoposide, and cisplatin; EP, etoposide and cisplatin; MET, metabolic equivalent task; VIP, etoposide, ifosfamide, and cisplatin; EORTC, European Organisation for the Research and Treatment of Cancer; QLQ-C30, Quality of Life Questionnaire Core; SF-36, Short Form-36; SCIN, Scale for chemotherapy induced neurotoxicity; QLQ-TC26, QLQ-TC26, EORTC Quality of Life Questionnaire - testicular cancer module; the Impact of Event Scale, SWED-QUAL, Swedish Health-Related Quality of Life Survey; GLQ-8, 8 linear analogue self-assessment scales; QLQ-CIPN20, EORTC quality of life questionnaire - chemotherapy-induced peripheral neuropathy; FACT-F, Functional Assessment of Cancer Therapy: Fatigue; MSAS-SF, Memorial Symptom Assessment Scale - Short form; RTOG, Radiation Therapy Oncology Group – recommended toxicity criteria.

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(p=0.003).[29] Oldenburg 2006 (N=684) found that lower proportions of men who had low-dose chemotherapy reported "high" SCIN scores (28–37%, compared to 63–72% in the high-dose chemotherapy group). "Low" SCIN scores were found in 53–54% of men in the low-dose group compared to 46–47% in the high-dose group.[19]

Regarding dose-induced ototoxicity, one study (N=812) found that among men treated with four cycles of bleomycin, etoposide, and cisplatin (BEP), there were significantly higher rates of tinnitus for those treated over three days as compared with five days (p=0.0002).[24] Oldenburg 2007 (N=238) also found that cumulative dose of cisplatin was significantly associated with tinnitus (p<0.001) and hearing impairment (p <0.001), along with the other neurotoxic side-effects noted above.

Differences in Neurotoxicity and Raynaud-Like Phenomena by Treatment Type

BEP seemed to be associated with some higher neurotoxicity than other regimens. The prevalence and severity of Raynaud's phenomenon after three cycles of BEP exceeded those for four cycles of etoposide, and cisplatin (EP).[34] Fung (N=952) also found higher toxicity associated with BEP; specifically that the type and prevalence of individual adverse health outcomes after EP x 4 cycles versus BEP X 3 cycles were similar (p=0. 05), except for Raynaud phenomenon (11.6% v 21.4%; P = 0.01), peripheral neuropathy (29.2% v 21.4%; p= 0.02), and obesity (25.5% v 33.0%; p= 0.04).[48]

Chemotherapy appeared to be associated with more neurotoxic symptoms compared to other types of treatment, including surveillance,[23,39] RPLND, or radiotherapy.[23,37] Neurotoxic symptoms were, however, associated with other treatments as well. Fossa 1996 found that although participants treated with radiotherapy or chemotherapy had the highest scores for neurological symptoms, Raynaud-like phenomena and ototoxicity, participants treated with surveillance also experienced these symptoms at lower levels.[27] Oldenburg 2006 (N=684) also found a higher proportion of irradiated patients with "pain, paresthesias in the feet/toes" compared to men who had surgery alone.[19]

Ototoxicity was also reported for different modalities. Oldenburg et al also found 10% of the radiotherapy group reported "very much" tinnitus or impaired hearing.[19] Compared to age-matched controls, the rate of hearing loss was worse for testicular cancer survivors treated with cisplatin.[42]

Functional and Symptom Scales

Seven studies reported differences in functional and symptom scales according to treatment modality[35,40,45,46] or higher doses of treatment,[24,26,32] at one or more assessment time points. Kim et al found that survivors diagnosed five or more years ago treated with chemotherapy had poorest scores (compared to radiotherapy and surgery) on the SF-36 physical (p=0.0032) and mental component scores (p=0.039), physical functioning (p=0.027), role-physical (p=0.0044), general health (p=0.0001), vitality (p=0.011), social functioning (p=0.016) and mental health scales (p=0.028).[35]

Two studies found that men treated with chemotherapy reported worse functioning (physical functioning, social functioning[45] and functional wellbeing[46]) and worse fatigue[45,46] compared to men who did not receive chemotherapy initially, but there were no between-group differences 12–18 months later in either study.

Functional and Symptom Scales by Chemotherapy Dose or Concurrent Treatment

Chemotherapy dose or concurrent treatment was related to higher levels of self-reported toxicity in three of the high-quality studies. An RCT by de Witt and colleagues (N=812) found significant differences in favour of three cycles of BEP (versus four cycles of BEP) for physical function (p=0.008), role function (p=0.03), cognitive function (p=0.04), fatigue (p=0.003), nausea/vomiting (p=0.008), appetite loss (p=0.001), and overall QOL (p=0.03) at three months which decreased to no difference at 12 months.[24] In a RCT by Fossa and colleagues (N=666), men randomised to four cycles of chemotherapy for three days had more nausea/vomiting as assessed by the QLQ-C30 compared to men who had three cycles for three days, at three months. The lowest mean nausea/vomiting scores were seen for the group who had three cycles for five days.[26] In another study of survivors diagnosed an average of 10 years ago, men who had chemotherapy + radical resection had higher levels of nausea/vomiting than men who had chemotherapy only (p=0.04), but results were not clinically significant.[40]

Functional and Symptom Scales Associated with Radiotherapy

Three high-quality studies reported the impact of radiotherapy on functional and symptom scales. In one study (N=625), significantly more patients receiving 30 Gy for 15 fractions (compared to men receiving 20 Gy for 10

fractions) reported moderate or severe lethargy (20% v 5%) and an inability to carry out their normal work (46% v 28%) four weeks after starting radiotherapy. However, by 12 weeks, levels in both groups were similar.[32] In a descriptive radiotherapy study (N=98), bowel side-effects were described. Diarrhoea was reported at a high grade by 4/99 patients (4%) while three patients (3%) reported a low grade of blood in the stools.[11]

Wortel 2015 (N=161) reported no impact on body image or problems with undressing in the presence of others in the first six months since radiotherapy treatment.

Studies Reporting No Differences by Treatment

Three high-quality studies found no effect on self-reported functioning and symptoms based on treatment. Oechsle (N=164) found no differences on any Memorial Symptom Assessment Scale–Short Form scale among survivors treated with surgery versus radiotherapy versus chemotherapy in a long-term follow-up analysis.[38] Miyake (N=102) found no significant differences in any SF-36 scale score between patients treated with chemotherapy versus surveillance who had not shown any evidence of disease for at least six months.[36] Flechtner found no significant differences on any QLQ-C30 scale at three-years post-treatment between men treated with BEP versus RPLND.[25]

Cognitive Functioning

Chemotherapy was significantly associated with cognitive problems in two of the 29 high-quality studies. Skaali and colleagues (N=122) found more severe cognitive problems in the first 12 months since diagnosis among men who had one cycle (29%) and multiple cycles (25%) of chemotherapy, compared to those who had no chemotherapy (3%).[41] Similarly, survivors who were on average 11 years post-diagnosis who had five or more cycles of chemotherapy were at increased risk of self-reported language difficulties as compared to men who had fewer cycles or no chemotherapy.[43]

Sexual Functioning

Five high-quality studies described the impact of treatment on sexual functioning. Only one of these studies found no relationship between type of treatment and modification of sexual life among survivors who were an average of 11 years since diagnosis.[31] The other four studies observed differences by treatment. Jonker-Poole (N=264) found that surveillance had the lowest impact on sexual functioning and activity among survivors who were a mean of 6.7 years post-diagnosis. Chemotherapy was associated with problems with libido (p=0.03), orgasm (p=0.010), ejaculation (p=0.04), and sexual activity (p=0.005) after age was adjusted for, among these survivors. Ejaculation problems were worse among men who had chemotherapy + RPLND compared to men who had radiotherapy (p<0.001) or chemotherapy (p=0.002).[33]

Similarly, Huddart (N=680) found that men who had chemo-radiotherapy more than five years previously were more likely to report less interest in sex (p=0.01) compared to men who had chemotherapy alone, radiotherapy or surveillance.[30] Men who had radiotherapy reported less sexual activity (p=0.051) and reduced sexual enjoyment (p=0.05) compared to surveillance. Survivors who had chemotherapy, as compared to men who had surveillance, reported more worries about fathering children (p=0.009).[30]

In a single-arm radiotherapy study, Wortel (N=161) found that the self-reported quality of men's erections decreased from post-orchidectomy to 6 months post-radiotherapy (p=0.016). No other impacts of radiotherapy were seen at six months post-radiotherapy for sexual interest (p=0.07), maintaining erections (p=0.08), or quality of spontaneous erections (p=0.88).[47] In another study of radiotherapy impacts (N=98), n=23 (23%) of participants reported a low degree of libido, 13 (13%) defined their sexual capacity as poor, 74 patients (75%) reported an erection sufficient for sexual intercourse, and 72 patients (73%) reported a good capacity to achieve orgasm. Sexuality was considered a significant problem by 11 patients (11%).[11]

Discussion

This review summarises the patient-reported symptoms, side-effects and functional impacts of common treatments for testicular cancer. In balance, it appears that chemotherapy is associated with higher levels of side-effect burden than other treatments, and the burden is increased with increasing dose of chemotherapy. Raynaud's phenomena and neurotoxic side-effects, such as hearing issues and peripheral neuropathy seemed to be associated more frequently and more intensely with chemotherapy than with other forms of treatment, although we did not conduct a meta-analysis to verify this statistically. Although only two high-quality studies that met our inclusion criteria studied the impact of treatment on cognitive functioning, both studies showed evidence of higher doses of

chemotherapy being associated with more cognitive problems.[41,43]

The evidence for differing impact of treatment on sexual functioning was mixed. Chemotherapy, alone or in combination with other modalities, was associated with lower sexual interest in two studies,[30,33] yet another study reported no difference in this regard.[31] Radiotherapy, alone or in combination with other modalities, was frequently associated with less interest in sex, reduced sexual activity and poorer-quality erections,[11,30,47] although no impact of radiotherapy on body image or undressing in front of others was found.[47] None of the included, high-quality studies explicitly examined the impact of a bilateral orchiectomy on sexual functioning.

Differences in functional and symptom scales according to treatment modality[35,40,45,46] or higher doses of treatment[24,26,32] were frequently reported. Nausea and vomiting were frequently reported by men who received chemotherapy, during active treatment and shortly after[24,26] or radical (retroperitoneal lymph node dissection) following cisplatin-based chemotherapy among survivors a median of 10 years since treatment-.[40] Chemotherapy was associated with worse physical functioning, social functioning,[45] functional wellbeing[46] and fatigue[45,46] compared to men who did not receive chemotherapy in the first six-months post-treatment.

Differences seen in results between studies may be an effect of different treatment regimens, but it is important to note that they may be an effect of methodological differences. There were 27 different PRO measures used across the 41 studies, and only 14 of these appeared to be validated, which may reflect the quality of these measures. Some of these measures focused exclusively on neurotoxic effects (SCIN, QLQ-CIPN20) whereas others focused on more general functional issues and side-effects (eg, SF-36, QLQ-C30, QLQ-TC26). Had the included studies measured the same set of PRO domains, our findings may have been different. The data collection time points also differed, depending on the specific research questions of the individual studies. We noted a trend for differences seen during active treatment, or shortly thereafter, to reduce or disappear over time.

We also note that most of the studies that met our inclusion criteria (36 of 41 studies in total, and 26 of the high-quality studies) included chemotherapy; therefore, our results may be skewed to reflect the burden associated with chemotherapy over other treatment modalities.

It is important to note that certain treatments featured in this review are no longer recommended in clinical practice guidelines, due to more effective treatments becoming available. For example, one study (which did not meet our quality criteria for inclusion in the narrative synthesis) reported use of vincristine,[49] which is no longer used. According to most guidelines,[3] BEP or EP chemotherapy is standard for all stages of testicular cancer. Moreover, improved surgical techniques have been found to preserve sexual function and reduce short- and long-term toxicities.[50,51] For instance, bilateral RPLND was associated with retrograde ejaculation; however, modified unilateral RPLND reduced the frequency of this problem. Radiotherapy doses, fields, indications, and use has diminished. Studies conducted before 2000, two of which are included in our narrative synthesis,[27,33] used higher doses and larger fields of radiotherapy, which may have contributed to more gastrointestinal or other toxicities.

The strengths of this study include a robust search strategy that was developed in collaboration with an academic librarian and pilot tested several times, and use of established and trusted review methods.[15,16] We limited the search to English articles, which means we may have missed some relevant, non-English literature; however, we do not anticipate that this would impact our findings, as previous research suggests.[52] We also note that many (n=27/41) of the included studies recruited participants from Western Europe. This is consistent with the incidence of testicular cancer being higher in Western Europe, as well as the UK, Australia and New Zealand.[2] We acknowledge the possibility that we may have missed relevant articles due to human error. We also note that there may have been overlap in the samples of Norwegian studies,[9,44] as these participants were recruited from the same program of research.

It can be difficult to collate and compare the PRO results of different studies due to variation in overall quality, designs, measures, analysis techniques and reporting formats. This is a recognised issue[53] and numerous PRO methodological researchers are taking steps to make PRO data more accessible and interpretable to readers, through the development of guidelines for design,[54] conduct,[55] analysis[56] and reporting[57] of PROs. We encourage researchers to read and adhere to these PRO guidelines when planning and conducting research on men with a history of testicular cancer with PROs. It is not always appropriate to recommend the same PRO measures for all studies, as the PROs of

importance to a particular clinical context are often nuanced and context-specific. Having a set of standard PROs appropriate to all cancers is helpful, with the addition of disease- or treatment-specific PROs as relevant, would be a great approach to improve transparency and interpretability of patient-centred outcomes. More importantly, involving patients in the development of measures ensures that key issues are addressed relating to the specific disease and treatment options, and that questions are acceptable to patients. We did not assess the development methodology of the measures included in this review; however, we do note that the EORTC PRO measures involve patients in their development.

Differences in follow-up time points for PRO assessment can also present challenges for interpretation. The survivorship studies in this review had very wide data collection windows. Although treatment side-effects may ease over time, reporting mean scores from participants at very different survivorship stages may be misleading. We chose to include data from studies of active treatment and survivorship to canvas the experience of testicular cancer treatment and recovery more comprehensively, and have noted the time since treatment where available, for transparency.

This review summarises the expected side-effects, both short-term and long-term, of treatments used commonly for testicular cancer. While many studies found that short-term adverse effects resolved within 12 months of treatment, there were clearly long-term effects, often dose-dependent, associated with chemotherapy and radiotherapy. It is widely acknowledged that patients have varying treatment preferences; while some prioritise length of life at all costs, others consider risk and fear of recurrence as well as quality of life to varying degrees. Offering information about all of these aspects upon considering treatment options allows patients, their families and clinicians to be informed, prepared and empowered to make treatment decisions suited to their preferences and personal situations. We hope that the findings of this review will assist this process.

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References

1. Chia VM, Quraishi SM, Devesa SS, Purdue MP, Cook MB, McGlynn KA. International trends in the incidence of testicular cancer, 1973–2002. *Cancer Epidemiol Biomarkers Prev*. 2010;19(5):1151–1159. doi:10.1158/1055-9965.EPI-10-0031
2. Park JS, Kim J, Elghiaty A, Ham WS. Recent global trends in testicular cancer incidence and mortality. *Medicine*. 2018;97(37):e12390. doi:10.1097/MD.0000000000012390
3. Oldenburg J, Fosså SD, Nuver J, et al. Testicular seminoma and non-seminoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2013;24(Suppl 6):vi125–32. doi:10.1093/annonc/mdt304
4. NIH National Cancer Institute. Cancer stat facts: testicular cancer; 2021. Available from: https://seer.cancer.gov/statfacts/html/testis.html. Accessed May 13, 2021.
5. Jacobsen KD, Theodorsen L, Fossa SD. Spermatogenesis after unilateral orchiectomy for testicular cancer in patients following surveillance policy. *J Urol*. 2001;165(1):93–96. doi:10.1097/00005392-200101000-00023
6. Shpunt I, Leibovici D, Ikher S, et al. Spermatogenesis in testicles with germ cell tumors. *Isr Med Assoc J*. 2018;20(10):642–644.
7. Donohue JP, Foster RS, Rowland RG, Bihrle R, Jones J, Geier G. Nerve-sparing retroperitoneal lymphadenectomy with preservation of ejaculation. *J Urol*. 1990;144(2 Pt 1):287–91; discussion 91–2. doi:10.1016/S0022-5347(17)39434-X
8. Rossen P, Pedersen AF, Zachariae R, von der Maase H. Sexuality and body image in long-term survivors of testicular cancer. *Eur J Cancer*. 2012;48(4):571–578. doi:10.1016/j.ejca.2011.11.029
9. Oldenburg J, Kraggerud SM, Brydoy M, Cvancarova M, Lothe RA, Fossa SD. Association between long-term neuro-toxicities in testicular cancer survivors and polymorphisms in glutathione-s-transferase-P1 and -M1, a retrospective cross sectional study. *J Transl Med*. 2007;5:1–8. doi:10.1186/1479-5876-5-70
10. Huddart RA, Norman A, Shahidi M, et al. Cardiovascular disease as a long-term complication of treatment for testicular cancer. *J Clin Oncol*. 2003;21(8):1513–1523. doi:10.1200/JCO.2003.04.173
11. Caffo O, Amichetti M, Tomio L, Galligioni E. Quality of life after radiotherapy for early-stage testicular seminoma. *Radiother Oncol*. 2001;59(1):13–20. doi:10.1016/S0167-8140(00)00264-4
12. Revicki DA, Osoba D, Fairclough D, et al. Recommendations on health-related quality of life research to support labeling and promotional claims in the United States. *Qual Life Res*. 2000;9(8):887–900. doi:10.1023/A:1008996223999
13. Food and Drug Administration. Guidance for industry: patient-reported outcome measures: use in medical product development to support labelling claims; 2009. Available from: http://www.fda.gov/downloads/Drugs/Guidances/UCM193282.pdf. Accessed May 13, 2021.
14. Rinecones O, Smith AB, Naher SK, Mercieca-Bebber R, Stockler M. An updated systematic review of quantitative studies assessing anxiety, depression, fear of cancer recurrence or psychological distress in testicular cancer survivors. *Cancer Manag Res*. 2021.

15. Moher D, Liberati A, Tetzlaff J, Altman DG; The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6(7):e1000097. doi:10.1371/journal.pmed.1000097
16. Kmet L, Cook LS, Lee R. Standard quality assessment criteria for evaluating primary research papers from a variety of fields AHFMRHTA initiative20040213. 2004.
17. Aaronson NK, Ahmedzai S, Bergman B, et al. The European organization for research and treatment of cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst*. 1993;85(5):365–376. doi:10.1093/jnci/85.5.365
18. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care*. 1992;30(6):473–483. doi:10.1097/00005650-199206000-00002
19. Oldenburg J, Fosså SD, Dahl AA. Scale for chemotherapy-induced long-term neurotoxicity (SCIN): psychometrics, validation, and findings in a large sample of testicular cancer survivors. *Qual Life Res*. 2006;15(5):791–800. doi:10.1007/s11136-005-5370-6
20. Sztankay M, Aaronson NK, Arraras JI, et al. International Phase IV validation study of an EORTC quality of life questionnaire for testicular cancer patients: the EORTC QLQ-TC26. *BMC Cancer*. 2018;18(1):1104. doi:10.1186/s12885-018-5036-8
21. Brorsson B, Ifver J, Hays RD. The Swedish health-related quality of life survey (SWED-QUAL). *Qual Life Res*. 1993;2(1):33–45. doi:10.1007/BF00642887
22. Sullivan M, Karlsson J, Bengtsson C, Furunes B, Lapidus L, Lissner L. "The Göteborg quality of life instrument"–a psychometric evaluation of assessments of symptoms and well-being among women in a general population. *Scand J Prim Health Care*. 1993;11(4):267–275. doi:10.3109/02813439308994842
23. Brydoy M, Oldenburg J, Klepp O, et al. Observational study of prevalence of long-term Raynaud-like phenomena and neurological side effects in testicular cancer survivors. *J Natl Cancer Inst*. 2009;101(24):1682–1695. doi:10.1093/jnci/djp413
24. de Wit R, Roberts JT, Wilkinson PM, et al. Equivalence of three or four cycles of bleomycin, etoposide, and cisplatin chemotherapy and of a 3- or 5-day schedule in good-prognosis germ cell cancer: a randomized study of the European organization for research and treatment of cancer genitourinary tract cancer cooperative group and the medical research council. *J Clin Oncol*. 2001;19(6):1629–1640. doi:10.1200/JCO.2001.19.6.1629
25. Flechtner HH, Fischer F, Albers P, Hartmann M, Siener R. Quality-of-life analysis of the German prospective multicentre trial of single-cycle adjuvant BEP Versus retroperitoneal lymph node dissection in clinical stage I nonseminomatous germ cell tumours. *Eur Urol*. 2016;69(3):518–525. doi:10.1016/j.eururo.2015.11.007
26. Fossa SD, de Wit R, Roberts JT, et al. Quality of life in good prognosis patients with metastatic germ cell cancer: a prospective study of the European organization for research and treatment of cancer genitourinary group/Medical research council testicular cancer study group (30941/TE20). *J Clin Oncol*. 2003;21(6):1107–1118. doi:10.1200/JCO.2003.02.075
27. Fossa SD, Moynihan C, Serbouti S. Patients' and doctors' perception of long-term morbidity in patients with testicular cancer clinical stage I. A descriptive pilot study. *Support Care Cancer*. 1996;4(2):118–128. doi:10.1007/BF01845761
28. Glendenning JL, Barbachano Y, Norman AR, Dearnaley DP, Horwich A, Huddart RA. Long-term neurologic and peripheral vascular toxicity after chemotherapy treatment of testicular cancer. *Cancer*. 2010;116(10):2322–2331. doi:10.1002/cncr.24981
29. Grimison PS, Stockler MR, Thomson DB, et al. Comparison of two standard chemotherapy regimens for good-prognosis germ cell tumors: updated analysis of a randomized trial. *J Natl Cancer Inst*. 2010;102(16):1253–1262. doi:10.1093/jnci/djq245
30. Huddart RA, Norman A, Moynihan C, et al. Fertility, gonadal and sexual function in survivors of testicular cancer. *Br J Cancer*. 2005;93(2):200–207. doi:10.1038/sj.bjc.6602677
31. Joly F, Heron JF, Kalusinski L, et al. Quality of life in long-term survivors of testicular cancer: a population-based case-control study. *J Clin Oncol*. 2002;20(1):73–80. doi:10.1200/JCO.2002.20.1.73
32. Jones WG, Fossa SD, Mead GM, et al. Randomized trial of 30 versus 20 Gy in the adjuvant treatment of stage I testicular seminoma: a report on medical research council trial TE18, European organisation for the research and treatment of cancer trial 30942 (ISRCTN18525328). *J Clin Oncol*. 2005;23(6):1200–1208. doi:10.1200/JCO.2005.08.003
33. Jonker-Pool G, van Basten JP, Hoekstra HJ, et al. Sexual functioning after treatment for testicular cancer: comparison of treatment modalities. *Cancer*. 1997;80(3):454–464. doi:10.1002/(SICI)1097-0142(19970801)80:3<454::AID-CNCR13>3.0.CO;2-W
34. Kerns SL, Fung C, Monahan PO, et al. Cumulative burden of morbidity among testicular cancer survivors after standard cisplatin-based chemotherapy: a multi-institutional study. *J Clin Oncol*. 2018;36(15):1505–1512. doi:10.1200/JCO.2017.77.0735
35. Kim C, McGlynn KA, McCorkle R, et al. Quality of life among testicular cancer survivors: a case-control study in the United States. *Qual Life Res*. 2011;20(10):1629–1637. doi:10.1007/s11136-011-9907-6
36. Miyake H, Muramaki M, Eto H, Kamidono S, Hara I. Health-related quality of life after chemotherapy for advanced germ cell tumors: a comparison of standard-dose and high-dose chemotherapy. *Int J Urol*. 2004;11(7):542–546. doi:10.1111/j.1442-2042.2004.00839.x
37. Mykletun A, Dahl AA, Haaland CF, et al. Side effects and cancer-related stress determine quality of life in long-term survivors of testicular cancer. *J Clin Oncol*. 2005;23(13):3061–3068. doi:10.1200/JCO.2005.08.048
38. Oechsle K, Hartmann M, Mehnert A, Oing C, Bokemeyer C, Vehling S. Symptom burden in long-term germ cell tumor survivors. *Support Care Cancer*. 2016;24(5):2243–2250. doi:10.1007/s00520-015-3026-9
39. Rossen PB, Pedersen AF, Zachariae R, von der Maase H. Health-related quality of life in long-term survivors of testicular cancer. *J Clin Oncol*. 2009;27(35):5993–5999. doi:10.1200/JCO.2008.19.6931
40. Schmidt AH, Hoyer M, Jensen BFS, Agerbaek M. Limited post-chemotherapy retroperitoneal resection of residual tumour in non-seminomatous testicular cancer: complications, outcome and quality of life. *Acta Oncol*. 2018;57(8):1084–1093. doi:10.1080/0284186X.2018.1449249
41. Skaali T, Fossa SD, Andersson S, et al. Self-reported cognitive problems in testicular cancer patients: relation to neuropsychological performance, fatigue, and psychological distress. *J Psychosom Res*. 2011;70(5):403–410. doi:10.1016/j.jpsychores.2010.12.004
42. Skalleberg J, Smastuen MC, Oldenburg J, Osnes T, Fossa SD, Bunne M. The relationship between cisplatin-related and age-related hearing loss during an extended follow-up. *Laryngoscope*. 2020;17:17.
43. Skoogh J, Steineck G, Stierner U, et al. Testicular-cancer survivors experience compromised language following chemotherapy: findings in a Swedish population-based study 3–26 years after treatment. *Acta Oncol*. 2012;51(2):185–197. doi:10.3109/0284186X.2011.602113
44. Sprauten M, Darrah TH, Peterson DR, et al. Impact of long-term serum platinum concentrations on neuro- and ototoxicity in Cisplatin-treated survivors of testicular cancer. *J Clin Oncol*. 2012;30(3):300–307. doi:10.1200/JCO.2011.37.4025
45. Vidrine DJ, Hoekstra-Weebers JE, Hoekstra HJ, Tuinman MA, Marani S, Gritz ER. The effects of testicular cancer treatment on health-related quality of life. *Urology*. 2010;75(3):636–641. doi:10.1016/j.urology.2009.09.053

46. Whitford HS, Kalinowski P, Schembri A, et al. The impact of chemotherapy on cognitive function: a multicentre prospective cohort study in testicular cancer. *Support Care Cancer*. 2019.
47. Wortel RC, Ghidey Alemayehu W, Incrocci L. Orchiectomy and radiotherapy for stage I-II testicular seminoma: a prospective evaluation of short-term effects on body image and sexual function. *J Sex Med*. 2015;12(1):210–218. doi:10.1111/jsm.12739
48. Fung C, Sesso HD, Williams AM, et al. Multi-institutional assessment of adverse health outcomes among North American testicular cancer survivors after modern cisplatin-based chemotherapy. *J Clin Oncol*. 2017;35(11):1211–1222. doi:10.1200/JCO.2016.70.3108
49. Dearnaley DP, Fossa SD, Kaye SB, et al. Adjuvant bleomycin, vincristine and cisplatin (BOP) for high-risk stage I non-seminomatous germ cell tumours: a prospective trial (MRC TE17). *Br J Cancer*. 2005;92(12):2107–2113. doi:10.1038/sj.bjc.6602624
50. Hanna N, Einhorn LH. Testicular cancer: a reflection on 50 years of discovery. *J Clin Oncol*. 2014;32(28):3085–3092. doi:10.1200/JCO.2014.56.0896
51. National Comprehensive Cancer Network. NCCN guidelines for testicular cancer version 1.2021; 2020. Available from: https://www.nccn.org/professionals/physician_gls/pdf/testicular.pdf. Accessed May 13, 2021.
52. Moher D, Pham B, Klassen TP, et al. What contributions do languages other than English make on the results of meta-analyses? *J Clin Epidemiol*. 2000;53(9):964–972. doi:10.1016/S0895-4356(00)00188-8
53. Bottomley A, Pe M, Sloan J, et al. Analysing data from patient-reported outcome and quality of life endpoints for cancer clinical trials: a start in setting international standards. *Lancet Oncol*. 2016;17(11):e510–e4. doi:10.1016/S1470-2045(16)30510-1
54. Calvert M, Kyte D, Mercieca-Bebber R, et al. Guidelines for inclusion of patient-reported outcomes in clinical trial protocols: the spirit-pro extension. *JAMA*. 2018;319(5):483–494. doi:10.1001/jama.2017.21903
55. Mercieca-Bebber R, Palmer MJ, Brundage M, Calvert M, Stockler MR, King MT. Design, implementation and reporting strategies to reduce the instance and impact of missing patient-reported outcome (PRO) data: a systematic review. *BMJ Open*. 2016;6(6). doi:10.1136/bmjopen-2015-010938
56. Coens C, Pe M, Dueck AC, et al. International standards for the analysis of quality-of-life and patient-reported outcome endpoints in cancer randomised controlled trials: recommendations of the SISAQOL Consortium. *Lancet Oncol*. 2020;21(2):e83–e96. doi:10.1016/S1470-2045(19)30790-9
57. Calvert M, Brundage M, Jacobsen PB, Schunemann HJ, Efficace F. The CONSORT patient-reported outcome (PRO) extension: implications for clinical trials and practice. *Health Qual Life Outcomes*. 2013;11:184. doi:10.1186/1477-7525-11-184

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